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# 1 **Higher frequency of dipeptidyl peptidase IV inhibitor intake in bullous pemphigoid** 2 **patients than in the French general population**

## 3 **Authors**

4 Marthe Plaquevent, M.D. <sup>(1)</sup>, Florence Tétart, M.D. <sup>(1)</sup>, Laurence Fardet, M.D., Ph.D. <sup>(2)</sup>,  
5 Saskia Ingen-Housz-Oro, M.D. <sup>(2)</sup>, Laurence Valleyrie-Allanore, M.D. <sup>(2)</sup>, Philippe Bernard,  
6 M.D., Ph.D. <sup>(3)</sup>, Vivien Hebert, M.D. <sup>(1)</sup>, Aude Roussel, M.D. <sup>(4)</sup>, Martine Avenel-Audran,  
7 M.D., Ph.D. <sup>(5)</sup>, Guillaume Chaby, M.D. <sup>(6)</sup>, Michel D'Incan, M.D., Ph.D. <sup>(7)</sup>, Marie-Christine  
8 Ferrier-Le-Bouedec, M.D. <sup>(7)</sup>, Sophie Duvert-Lehembre, M.D. <sup>(8)</sup>, Catherine Picard-Dahan,  
9 M.D. <sup>(9)</sup>, Geraldine Jeudy, M.D. <sup>(10)</sup>, Evelyne Collet, M.D. <sup>(10)</sup>, Bruno Labeille, M.D., Ph.D.  
10 <sup>(11)</sup>, Cécile Morice, M.D. <sup>(12)</sup>, Marie-Aleth Richard, M.D., Ph.D. <sup>(13)</sup>, Isabelle Bourgault-  
11 Villada, M.D., Ph.D. <sup>(14)</sup>, Noémie Litrowski, M.D. <sup>(15)</sup>, Corina Bara, M.D. <sup>(16)</sup>, Emmanuel  
12 Mahe, M.D. <sup>(17)</sup>, Catherine Prost-Squarcioni, M.D., Ph.D. <sup>(18)</sup>, Marina Alexandre, M.D. <sup>(18)</sup>,  
13 Gaëlle Quereux, M.D., Ph.D. <sup>(19)</sup>, Claire Bernier, M.D. <sup>(19)</sup>, Angèle Soria, M.D. <sup>(20)</sup>, Domitille  
14 Thomas-Beaulieu, M.D. <sup>(21)</sup>, Christine Pauwels, M.D. <sup>(21)</sup>, Olivier Dereure, M.D., Ph.D. <sup>(22)</sup>,  
15 Jacques Benichou, M.D., Ph.D. <sup>(23)</sup>, Pascal Joly, M.D., Ph.D. <sup>(1)</sup> and the French Investigators  
16 for Skin Adverse Reaction to Drugs (FISARD) and the French study group on autoimmune  
17 bullous skin diseases.

18 (1) Department of Dermatology, Rouen University Hospital and INSERM U1234, Centre de  
19 référence des maladies bulleuses autoimmunes, Normandie University, Rouen.

20 (2) Department of Dermatology, AP-HP, Henri Mondor Hospital, Créteil.

21 (3) Department of Dermatology, University of Reims, Reims.

22 (4) Department of Dermatology, Orleans Hospital, Orléans.

23 (5) Department of Dermatology, University of Angers, Angers.

24 (6) Department of Dermatology, University of Amiens, Amiens

25 (7) Department of Dermatology, University of Clermont-Ferrand, Clermont-Ferrand.

26 (8) Department of Dermatology, University of Lille, Lille.

27 (9) Department of Dermatology of Bichat Hospital, University of Paris X, Paris.

28 (10) Department of Dermatology Dijon University Hospital, Dijon.

29 (11) Department of Dermatology, University of Saint Etienne, Saint Etienne.

30 (12) Department of Dermatology, University of Caen, Caen.

31 (13) Department of Dermatology, Assistance Publique des Hôpitaux de Marseille, Aix  
32 Marseille University, UMR 911, INSERM CRO2, Marseille.

33 (14) Department of Dermatology, Ambroise Paré Hospital, Boulogne-Billancourt.

34 (15) Department of Dermatology, Jacques Monod Hospital, Montivilliers.

35 (16) Department of Dermatology, Le Mans General Hospital, Le Mans.

36 (17) Department of Dermatology, Argenteuil Hospital, Argenteuil.

37 (18) Department of Dermatology, University of Paris XIII, Bobigny.

- 1 (19) Department of Dermatology, University of Nantes, Nantes.  
2 (20) Department of Dermatology and Allergology, Tenon Hospital, Paris.  
3 (21) Department of Dermatology, Poissy-Saint Germain Hospital, Saint-Germain-en-Laye.  
4 (22) Department of Dermatology, University of Montpellier, Montpellier.  
5 (23) Department of Biostatistics, Rouen University Hospital and INSERM U1219, Normandie  
6 University, Rouen.

7

8 **Corresponding author**

9 Marthe PLAQUEVENT MASTROIENI  
10 CHU de Rouen, Clinique dermatologique  
11 1 Rue de Germont  
12 76000 ROUEN  
13 Telephone: +33(0)232 888 054  
14 Fax: +33(0)232 888 055  
15 Email: martheplaquevent@orange.fr

16

17 **Short title:** Gliptin-associated bullous pemphigoid

18 **Abbreviations**

- 19 ALD: Affection de Longue Durée (presence of chronic diseases)  
20 BP: Bullous Pemphigoid  
21 CI: Confidence Interval  
22 DPP4: DiPeptidyl Peptidase-4  
23 EGB: Echantillon Généraliste des Bénéficiaires (database of the National French Health  
24 Insurance Agency)  
25 ELISA: Enzyme-Linked ImmunoSorbent Assay  
26 IQR: Interquartile Range  
27 OR: Odds Ratio

## 1 **Summary**

2 Dipeptidyl-peptidase-IV-inhibitors have been suspected to induce bullous pemphigoid (BP).  
3 The objective of this study was to compare the observed frequency of gliptin intake in a large  
4 sample of 1787 BP patients diagnosed between 2012 and 2015 in France, with the expected  
5 frequency after indirect age standardization on 225412 individuals extracted from the  
6 database of the National Healthcare Insurance Agency. The secondary objective was to assess  
7 the clinical characteristics and the course of gliptin-associated BP depending on whether  
8 gliptin was continued or stopped. The observed frequencies of intake of the whole gliptin  
9 class and that of vildagliptin in the BP population were higher than those in the general  
10 population after age standardization (whole gliptin class: 6.0% (95% confidence interval  
11 (CI)=4.9-7.1%) versus 3.6%, observed to expected-drug intake ratio=1.7 (95% CI=1.4-  
12 2.0), $p<0.0001$ ; vildagliptin=3.3% (95% CI=2.5-4.1%) versus 0.7%, ratio=4.4 (95% CI=3.5-  
13 5.7), $p<0.0001$ ). The association of any gliptin+metformin was also higher than in the general  
14 population, ratio=1.8 (95% CI=1.3-2.4,  $p<0.0001$ ). Gliptin-associated BP had no specific  
15 clinical characteristics. Gliptin was stopped in 48 cases (45.3%). Median duration to achieve  
16 disease control, rate and delay of relapse were not different whether gliptin was stopped or  
17 continued. This study strongly supports the association between gliptin intake, particularly  
18 vildagliptin, and the onset of BP.

19

1

## 2 INTRODUCTION

3 Bullous pemphigoid (BP) is the most frequent autoimmune subepidermal blistering disease.  
4 Its incidence has been estimated in France at 21.7 cases per million inhabitants overall, and  
5 162 cases per million inhabitants in people older than 70 years (Joly et al., 2012). The main  
6 risk factors for BP are debilitating neurological disorders especially multiple sclerosis and  
7 dementia, and drug intake (Bastuji-Garin et al., 2011, Cordel et al., 2007, Langan et al., 2011,  
8 Taghipour et al., 2010). Drug classes associated with the occurrence of BP are diuretics and  
9 neuroleptics. More recently, dipeptidyl peptidase-4 (DPP4) inhibitors also called gliptins have  
10 been reported to be associated with increased BP incidence (Bastuji-Garin et al., 1996,  
11 Bastuji-Garin et al., 2011, Cordel et al., 2007, Lloyd-Lavery et al., 2013).

12 Gliptins were approved in 2006 for the treatment of diabetes mellitus. They include  
13 sitagliptin, vildagliptin, saxagliptin, alogliptin and linagliptin. The main cutaneous side effects  
14 reported with gliptins are cutaneous eruptions, pruritus, urticarial reactions and some severe  
15 but rare reactions such as toxic epidermal necrolysis or anaphylaxis (Andukuri et al., 2009,  
16 Banerji et al., 2010, Desai et al., 2010, Gerrald et al., 2012, Scheen et al., 2010). Forty-one  
17 case reports and small case series of gliptin-associated BP have been reported since 2011  
18 (Aouidad et al., 2013, Attaway et al., 2014, Béné et al., 2015, Esposito et al., 2017, Fania et  
19 al., 2017, Garcia et al., 2016, Haber et al., 2016, Keseroglu et al., 2016, Mendonça et al.,  
20 2016, Pasmatzis et al., 2011, Sakai et al., 2017, Schaffer et al., 2017, Skandalis et al., 2012,  
21 Yoshiji et al., 2017). Additionally, two case-non-case studies using Pharmacovigilance  
22 Databases reported a signal for an increased risk of bullous pemphigoid during DPP-IV  
23 inhibitor exposure (Béné et al., 2016, Garcia et al., 2016). Recently, two retrospective case-  
24 control studies comparing the frequency of gliptin intake in BP patients with diabetes and in

1 control patients with diabetes but without BP, and a Finnish study comparing the frequency of  
2 gliptin intake in a BP population and in a control population of patients with basal cell  
3 carcinoma, have suggested an association between this drug class and the occurrence of BP  
4 (Benzaquen et al., 2017, Kridin and Bergman, 2018, Varpuluoma et al., 2018). However,  
5 none of these studies have compared the frequency of gliptin intake in a population of BP  
6 patients with that in the general population, which is essential since the prevalence of diabetes  
7 mellitus in the general population increases with age (involving 20% of men and 14% of  
8 women aged 75 to 84 years in France), and since gliptins are commonly prescribed in elderly  
9 diabetic patients (Doucet et al., 2016, Mandereau-Bruno and Fosse-Edorh, 2017). The effect  
10 of gliptin withdrawal was recently studied in 19 patients with gliptin-associated BP  
11 (Benzaquen et al., 2017). After an initial CS treatment, no further therapy was necessary in  
12 these patients after DPP4i withdrawal to obtain BP remission, suggesting a beneficial effect of  
13 gliptin withdrawal, which would be of major importance in clinical practice. Therefore, the  
14 main objective of this study was to compare the observed frequency of gliptin intake in a  
15 large sample of 1787 BP patients referred to the 21 dermatology departments of the French  
16 Study Group on Auto Immune Blistering Diseases, with that expected from indirect age  
17 standardization on a large sample of 225400 patients older than 50 years extracted from the  
18 database of the National Healthcare Insurance Agency.

19 Moreover, we assessed the clinical characteristics and the course of gliptin-associated BP  
20 depending on whether gliptin was continued or stopped.

21

# 1 **RESULTS**

## 2 **BP patients characteristics**

3 From January 1<sup>st</sup>, 2012 to December 31<sup>st</sup>, 2015, 1787 cases of BP were recorded. Among  
4 these, 108 (6.0%; 95% confidence interval (CI), 4.9-7.1%) were gliptin users. The main  
5 clinical characteristics and comorbidities of the 108 BP patients taking gliptins are shown in  
6 Table 1. The mean age (+/- standard deviation) of patients was  $77.9 \pm 9.3$  years. The  
7 male/female sex ratio was 1.16. Neurological comorbidities were found in 34 cases (31.5%).  
8 Fifty-six patients (51.9%) had moderate BP ( $\leq 10$  new blisters per day), 44 patients (40.7%)  
9 had severe BP ( $> 10$  new blisters per day) and 8 patients (7.4%) had localized or atypical BP  
10 (Table 1). The mean number of daily new blisters was  $36.9 \pm 73.2$  per day. Vildagliptin and  
11 sitagliptin were the most frequently used gliptins and were reported in 59 cases (54.6%) and  
12 44 cases (40.7%), respectively. Saxagliptin was prescribed in 5 cases (4.7%) only. The  
13 median delay (interquartile range (IQR)) between initiation of gliptins and the diagnosis of  
14 BP was 14.8 months (6.0-26.7 months). One hundred and three patients were initially treated  
15 with topical corticosteroids alone or associated with prednisone and / or immunosuppressants  
16 / immunomodulants. No patient was treated by gliptin withdrawal alone. In case of gliptin  
17 withdrawal, an associated topical or systemic treatment was always carried out. Rechallenge  
18 with the culprit gliptin was never performed.

## 19 **Expected frequencies of gliptin intake in BP patients from indirect age standardization** 20 **on the EGB sample and comparison with observed frequencies**

21 The observed frequency of the whole gliptin class intake and that of vildagliptin, sitagliptin  
22 and saxagliptin in the BP population, and the corresponding expected frequencies after  
23 indirect age standardization on the French general population (EGB sample) are reported in  
24 Table 2. After age standardization, the observed frequency of intake of the whole gliptin class

1 and that of vildagliptin were higher than expected in BP patients (whole gliptin class: 6.0%  
2 (95% confidence interval (CI), 4.9-7.1%) versus 3.6%,  $p < 0.0001$ ); vildagliptin: 3.3% (95%  
3 CI, 2.5-4.1%) versus 0.7%,  $p < 0.0001$ ), corresponding to an observed to expected drug intake  
4 frequency ratio of 1.7 (95% CI, 1.4-2.0) for the whole gliptin class, and 4.4 (95% CI, 3.3-5.7)  
5 for vildagliptin).

6 We then assessed the potential effect of metformin as a co-triggering factor of BP. Since we  
7 could only record the intake of preparations associating metformin + gliptin as a single  
8 medication in the general population, we compared the observed and expected frequencies of  
9 drugs containing this association in the BP population. Interestingly, the associations  
10 metformin + all gliptins, and metformin + vildagliptin were 1.8-fold (2.6% versus 1.4%,  
11  $p < 0.0001$ ) and 4.5-fold (1.9% versus 0.4%,  $p < 0.0001$ ) more frequently prescribed in the BP  
12 population than expected frequencies in the general population after age standardization  
13 (Table 2).

#### 14 **Clinical course of gliptin-associated BP depending on whether gliptin was continued or** 15 **withdrawn**

16 Information on gliptin withdrawal or continuation could be recorded in 106 of the 108  
17 patients who used gliptins. The median follow-up duration of patients (including deceased  
18 patients) after BP diagnosis was 9.9 months (interquartile range (IQR):1.0-21.2 months).  
19 Gliptin was continued in 58 patients (54.7%) and stopped in 48 cases (45.3%). The mean  
20 number of daily new blisters ( $43.0 \pm 90.9$  versus  $32.2 \pm 56.6$ ;  $p = 0.51$ ) and anti-BP180  
21 ( $116.9 \pm 88.1$  UA/ml versus  $114.4 \pm 84.7$  UA/ml;  $p = 0.95$ ), and anti-BP230 antibody ELISA  
22 values ( $33.3 \pm 45.8$  UA/ml versus  $53.1 \pm 60.6$ ;  $p = 0.090$ ) were not different between the group of  
23 patients in whom gliptins were stopped and the group of patients in whom gliptins were  
24 continued. The median delay between BP diagnosis and gliptin withdrawal in these latter  
25 patients was 12.0 days (IQR,1.0-71.0). The mean initial dose of clobetasol propionate cream



1 received by patients in whom gliptin was stopped was  $27.7 \pm 6.8$  g per day and that of patients  
2 who continued to take gliptin was  $27.3 \pm 8.4$  g per day ( $p=0.93$ ). Methotrexate was associated  
3 with topical corticosteroids in 6 and 4 cases, respectively.

4 The median duration to achieve disease control was not different whether gliptin was stopped,  
5 15.0 days (IQR, 5.0-31.5) or continued, 14.0 days (IQR, 5.0-30.0), ( $p=0.95$ ). Information  
6 about the occurrence of a first relapse was recorded in 74 cases. The rate and delay of relapse  
7 were not different whether gliptin was stopped (relapse rate, 17/39 (43.6%), delay, 4.8 months  
8 (IQR, 2.2-10.3)) or continued (relapse rate, 13/35 (37.1%), delay, 5.8 months (IQR, 3.0-14.0))  
9 ( $p=0.63$  and  $p=0.90$ , respectively).

10 Since we observed a wide variation in the delay of gliptin withdrawal (IQR, 1.0-71.0 days), we  
11 then assessed the relapse rate of BP patients depending on whether gliptin was stopped early  
12 or late after BP diagnosis. We arbitrarily chose a cut-off delay of more or less than one month  
13 between BP diagnosis and gliptin withdrawal, which resulted in a median delay between  
14 diagnosis of BP and gliptin withdrawal of 2.0 days (IQR, 1.0-10.0) in the “early gliptin  
15 withdrawal” subgroup and 4.0 months (IQR, 1.9-11.8) in the “late gliptin withdrawal”  
16 subgroup. No difference in the rate of relapse (10/23 (43.5%) versus 7/16 (43.8%);  $p=0.98$ ),  
17 or the delay of relapse (3.6 months (IQR, 1.3-7.5) versus 9.9 months (IQR, 4.0-15.5);  $p=0.17$ )  
18 was evidenced depending on whether gliptin was stopped, respectively, early or late after BP  
19 diagnosis.

20 Since vildagliptin and sitagliptin accounted for the majority of cases in the present study, we  
21 further investigated the delay of disease control and the rate of relapse depending on whether  
22 vildagliptin and sitagliptin were stopped or continued after BP diagnosis. Table 3 shows that  
23 no statistically significant difference in the delay of disease control, or the rate and delay of

1 relapse could be evidenced whether vildagliptin and sitagliptin were stopped or continued  
2 after BP diagnosis.

3

#### 4 **DISCUSSION**

5 The present study clearly demonstrated an association between gliptin intake and the onset of  
6 BP, since the frequency of gliptin intake was 1.7-fold more frequently observed in a large  
7 population of 1787 BP patients (6.0%), than expected from indirect age standardization  
8 (3.6%) on a sample of 225400 patients representative of the general population in France. The  
9 association between BP and vildagliptin intake was even higher than with the whole gliptin  
10 class, with an observed to expected drug intake frequency ratio of 4.4. Such an association  
11 with vildagliptin has been suggested by two pharmacovigilance studies which reported a  
12 disproportionately high number of declared cases of BP associated with vildagliptin relative  
13 to other drugs (Béné et al., 2016, Garcia et al., 2016). Two recent case-control studies also  
14 reported an association with vildagliptin which was taken by 23.0% and 29.3% of 61 and 82  
15 diabetic patients with BP versus 4.1% and 4.3% of 122 and 328 diabetic control patients  
16 respectively, resulting in adjusted ORs of 3.57 and 10.67, respectively (Benzaquen et al.,  
17 2017, Kridin and Bergman, 2018). As in these case-control studies, we did not evidence a  
18 statistically significant association with sitagliptin, or saxagliptin in the present study.  
19 Interestingly, the 6% versus 3.6% frequencies of gliptin intake that we observed in the BP and  
20 the general populations from the present study were close to the 6.5% and 2.0% frequencies  
21 observed in the BP population and a control population of patients with basal cell carcinoma  
22 in the Finnish study (Varpuluoma et al., 2018).

23 Benzaquen et al. suggested that gliptin withdrawal may have a favourable impact on the  
24 outcome of BP in diabetic patients, as 95% of them achieved clinical remission after gliptin

1 withdrawal and the start of a first-line treatment (Benzaquen et al., 2017). However, since  
2 most patients in their study were treated with high potency topical corticosteroids, which have  
3 been reported consistently to induce between 95% and 100% of complete remission (Joly et  
4 al., 2002, Joly et al., 2009), we feel that this statement must be interpreted cautiously.

5 Indeed, we found in the literature 35 cases of gliptin associated BP, in which the authors  
6 considered that stopping gliptin had a favorable effect on the course of BP. Most cases  
7 corresponded to persistent complete remission after gliptin withdrawal. However, we found  
8 only one case of partial remission of BP after gliptin withdrawal, without initial CS therapy.  
9 All other patients including the latter were treated with oral or systemic CS to achieve  
10 complete remission. According to the fact that all patients in our study were also treated with  
11 high potency topical corticosteroids or systemic treatments, we did not observe any difference  
12 in the delay of disease control, whether gliptin was stopped (median 15.0 days) or continued  
13 (median 14.0 days). We then assessed the relapse rate depending on whether gliptin was  
14 continued or stopped, and in the latter subgroup, depending on whether gliptin was stopped  
15 early or late after BP diagnosis. Interestingly, the 43.6% versus 37.1%, and 43.5% versus  
16 43.8% rates of relapse that we observed in these subgroups were not statistically different, and  
17 were in fact, very close to the 35% to 43% relapse rates that we previously reported in two  
18 large series of 700 BP patients treated with topical or oral corticosteroids (Joly et al., 2002,  
19 Joly et al., 2009). In our opinion, these findings do not support the previously suggested  
20 favourable impact of gliptin withdrawal on the outcome of BP patients.

21 Apart from a slightly younger age, we did not evidence any clinical particularities of patients  
22 with gliptin-associated BP, as compared with previous series reporting “usual” BP in France,  
23 irrespective of drugs used (Cordel et al., 2007, Joly et al., 2002, Joly et al., 2009).  
24 Neurological disorders were associated in 31.5% of patients from the present series versus  
25 36% in the study by Cordel et al. who first reported the association of BP and neurological

1 disorders (Cordel et al., 2007). Extensive, moderate and localized / atypical non-bullous types  
2 of BP accounted for 40.7%, 51.9% and 7.4% respectively, which corresponds to the usual  
3 presentation of clinical types of BP in France (Joly et al., 2012), and does not support the  
4 previously reported over representation of mild and pauci- inflammatory subtypes among  
5 gliptin-associated BP (Fania et al., 2017, Izumi et al., 2016, Sakai et al., 2017). We did not  
6 observe the borderline significant higher mucosal involvement found in the study by Kridin  
7 and Bergman (2018). Seventy percent of the tested sera recognized the NC16A domain of  
8 BP-180 by ELISA, which is in accordance with the 53% to 96% sensitivity of the BP-180  
9 ELISA reported in the literature (Chan et al., 2003, Charneux et al., 2011, Giudice et al.,  
10 1994, Kobayashi et al. 2002, Roussel et al., 2011, Sakuma-Oyama et al., 2004, Tampoia et al.,  
11 2009, Thoma-Uszynski et al., 2004, Zillikens et al., 1997), and the 65.8% rate of anti-BP180-  
12 NC16A antibodies reported by Kawaguchi et al. (2018) in 32 BP patients taking gliptins.  
13 Conversely, only 38% of sera from patients with gliptin associated BP recognized BP-230 by  
14 ELISA, which is lower than the 48% to 81.5% sensitivity of the BP-230 ELISA assay  
15 reported with “usual” BP sera (Blöcker et al., 2012, Charneux et al., 2011, Keller et al., 2016,  
16 Roussel et al., 2011, Sárdy et al., 2013, Tampoia et al., 2009, Thoma-Uszynski et al., 2004).  
17 We did not test these sera on epitopes located on the midportion of BP-180, which have been  
18 reported to be recognized by 7 of the 14 cases (50.0%) of sera from patients with gliptin-  
19 associated BP (Izumi et al., 2016).

20 The potential effect of metformin as a co-triggering factor of BP was not analysed in the case-  
21 control study of Benzaquen et al. (2017). Kridin and Bergman (2018) reported that the  
22 association of the use of DPP-4 inhibitor and BP was independent of the use of metformin.  
23 Conversely, Varpuluoma et al. (2018) showed that whereas metformin monotherapy was not  
24 associated with BP, metformin plus vildagliptin or sitagliptin was associated with an  
25 increased risk of BP, with respective adjusted ORs of 6.71 and 2.40 relative to a control

1 population of patients with basal cell carcinoma. We also observed in the present study, a  
2 between two- to almost five-fold higher frequency of the association of metformin with all  
3 gliptins or vildagliptin intake in the BP population than in the general population after indirect  
4 age standardization. Our findings might suggest a potential effect of metformin as a co-  
5 triggering factor of BP, whereas, Varpuluoma et al. suggested that in BP cases diagnosed  
6 during metformin-vildagliptin combination therapy, metformin could be safely continued  
7 during withdrawal of vildagliptin. Further studies are necessary to determine the exact role of  
8 metformin in the occurrence of gliptin-associated BP.

9 The main strengths of this study are the large population of 1787 patients with BP, and the  
10 comparison with a sample of 225400 patients from the “Echantillon Généraliste des  
11 Bénéficiaires” (EGB) database which is representative of the general population in France. A  
12 selection bias in the BP population is unlikely in this multicenter study since it was performed  
13 in 21 secondary and tertiary care dermatology departments of the French Study Group on  
14 Auto Immune Blistering Diseases and recruitment was exhaustive in all these centers. A recall  
15 bias is a common problem in retrospective studies, especially those involving elderly subjects  
16 who may suffer from memory impairment. However, since all BP patients are hospitalized in  
17 an out-patient or in-patient hospitalization unit in France, drug intake information was  
18 systematically verified from the hospital pharmacy computerized databases, which makes  
19 recall bias, whether differential or not, very unlikely in this study. A confounding (indication)  
20 bias is possible, since the data in the literature reporting the association diabetes-BP are  
21 contradictory (Bastuji-Garin et al., 2011; Kibsgaard et al., 2017, Ren et al., 2017, Taghipour  
22 et al., 2010). The absence of difference in the course of BP depending on whether gliptins  
23 were stopped or not might be due to a lack of statistical power. Indeed despite the fact that our  
24 cohort of 108 BP patients taking gliptins is the largest reported so far, the analyses comparing

1 risks of relapse between patients continuing gliptin intake and those stopping gliptin intake  
2 were calculated on a small population of patients (35 versus 39).

3 Finally, despite the retrospective design of the study which can be considered as a limitation,  
4 information on gliptin withdrawal or continuation could be recorded in all but two patients.

5 The pathogenesis of gliptin-associated BP remains unclear. Pathophysiological hypotheses  
6 have been proposed in a recent report (Benzaquen et al., 2017). DPP4 inhibition could  
7 enhance the activity of proinflammatory chemokines, like eotaxin, promoting eosinophil  
8 activation in the skin (Forssmann et al., 2008). Alternatively, gliptin intake, which blocks the  
9 transformation of plasminogen into plasmin, could result in the inhibition of the cleavage of  
10 BP-180 by plasmin, thus affecting its antigenicity and / or its function (Izumi et al., 2016).

11 In conclusion, this study confirms the association between gliptin intake, particularly  
12 vildagliptin, and the onset of BP. In view of the seriousness of BP, this risk and the known  
13 benefits of gliptins should be considered when devising a treatment strategy for elderly  
14 diabetic patients. Since patients with gliptin-associated BP do not seem to have a specific  
15 clinical presentation, or a particular course after gliptin withdrawal, it is likely that gliptins  
16 can trigger BP in high risk elderly diabetic patients, rather than really inducing BP, which is  
17 susceptible to spontaneous regression after gliptin withdrawal (Wolf et al., 1991).

18

## 19 **PATIENTS AND METHODS**

### 20 **Patients**

21 All BP patients consulting in the 21 Dermatology Departments of the French Study Group on  
22 Auto Immune Bullous Skin Diseases from January 1<sup>st</sup>, 2012 to December 31<sup>st</sup>, 2015 were  
23 included. Diagnosis of BP was made according to clinical and histological criteria (Courville  
24 et al, 2000, Joly et al., 2004, Kershenovich et al., 2014, Vaillant et al., 1998) and positive

1 direct immunofluorescence examination of a skin biopsy specimen showing linear deposits of  
2 IgG and / or C3 along the dermal epidermal junction (Feliciani et al, 2015). Anti-BP180 and  
3 anti-BP230 antibody titers were measured using a commercially available ELISA assay  
4 (Euroimmune, Germany) using the cut off values proposed by the manufacturer (20 UA/ ml).  
5 According to the French law, this retrospective study did not require the approval of an  
6 Ethics' committee, nor patients' informed consent.

### 7 **Assessment of gliptin intake**

8 ***Population of BP patients:*** Almost all BP patients end up being hospitalized in an out-patient  
9 or in-patient unit in France. Gliptin intake was therefore recorded from patients' medical files  
10 and systematically verified from the hospital pharmacy computerized prescription database.  
11 The delay between gliptin initiation and BP diagnosis, and the delay between BP diagnosis  
12 and gliptin withdrawal were also recorded from patients' medical files.

13 ***General population:*** We assessed gliptin intake in the French general population from the  
14 French reimbursement database "Echantillon Généraliste des Bénéficiaires" (EGB) that we  
15 accessed thanks to a successful request to the "Institut des Données de Santé" (French Health  
16 Data Institute). Gliptin intake in the general population was documented for the whole gliptin  
17 class and for each gliptin separately (sitagliptin, vildagliptin and saxagliptin), by age class,  
18 between January 1<sup>st</sup>, 2012 and December 31<sup>st</sup>, 2015. Approximately 90% of the French  
19 population is covered by the national healthcare insurance system. The EGB is a permanent  
20 representative sample of the population benefiting from the French healthcare insurance  
21 system. It is obtained by 1/97<sup>th</sup> random sampling with stratification on sex and age. For all  
22 beneficiaries, it consists of the exhaustive recording of drug reimbursements, with  
23 identification of medication packs, including the number and dosage strengths of treatment  
24 units. The database also contains information on socio-demographic features, hospitalization  
25 data (diagnoses and dates) and the presence of certain chronic diseases (*Affections de Longue*

1 *Durée*, ALD, an administrative status allowing full reimbursement of healthcare for a given  
2 condition, e.g., diabetes, cancer, psychosis). Details on the EGB scheme have been previously  
3 described (Bénard-Larivière et al., 2015, Bénard-Larivière et al., 2017).

#### 4 **Statistical analysis**

##### 5 *Primary objective*

6 The observed frequency of gliptin intake with its 95% confidence interval was calculated in  
7 BP patients and compared with the expected frequency after indirect age standardization on  
8 the French general population (Schokkaert and Van de Voorde, 2009). Namely, the expected  
9 proportion of BP patients with gliptin intake was obtained from applying age-specific  
10 proportions of gliptin intake in the general population (as obtained from the EGB sample) to  
11 the BP population, thus accounting for the age distribution in the BP population and age-  
12 specific gliptin intake frequencies in the general population. Then, observed and expected  
13 proportions of BP patients with gliptin intake were compared for the whole gliptin class and  
14 for each medication separately (sitagliptin, vildagliptin and saxagliptin) as well as  
15 preparations associating these drugs with metformin, using a one degree of freedom  
16 goodness-of-fit chi-square test. Finally, ratios of observed to expected numbers of BP patients  
17 with gliptin intake were estimated and corresponding 95% confidence intervals were obtained  
18 based on the log transformation. All tests were considered significant for a p value < 0.05.

##### 19 *Secondary objectives*

20 The criteria why gliptins were stopped depended on whether investigators were aware of the  
21 risk associated with gliptin intake, and convinced of the potential benefit of stopping gliptins.  
22 This number increased from the beginning of the study in 2012 to the end of the study in  
23 2015. Characteristics of BP course, i.e., delay of disease control, relapse (yes, no) and delay  
24 of relapse (among relapsing patients) were compared within the group of BP patients who had



1 used gliptin according to whether gliptin was stopped or continued, using the Wilcoxon-  
2 Mann-Whitney test or Pearson's chi-square test, as appropriate.

3

4 Softwares Microsoft Excel (Microsoft Office, Redmond, WA, USA, Version 2007) and  
5 StatXact (Cytel Software Corporation, Cambridge, MA, USA, Version 7) were used for  
6 statistical analyses.

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## 10 **CONFLICT OF INTEREST**

11 The authors state no conflict of interest.

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1 **Table 1. Clinical and immunological characteristics of the 108 patients with Bullous**  
 2 **Pemphigoid taking gliptins.**

	n (%)
Gender	
Male	58 (53.7)
Female	50 (46.3)
Mean age $\pm$ SD (years)	77.9 $\pm$ 9.3
Neurological disorders	34 (31.5)
Dementia	21 (19.4)
Stroke	16 (14.8)
Parkinson's disease	3 (2.8)
Multiple sclerosis	1 (0.9)
Peripheral neuropathy	1 (0.9)
Bullous Pemphigoid extent	
Severe (>10 new blisters/day).	44 (40.7)
Moderate ( $\leq$ 10 new blisters/day)	56 (51.9)
Atypical (localized or non-bullous)	8 (7.4)
Clinical presentation	
Eczematous	54 (50.0)
Urticarial	53 (49.1)
Including eczematous and urticarial	29 (26.9)
Pruritus	103 (95.4)
Blood eosinophilia <sup>1</sup>	46 (46.9)
Anti-BP230 antibodies <sup>2</sup>	22 (37.9)
ELISA value (mean $\pm$ SD)	43.2 $\pm$ 54.0 UA/ml
Anti-BP180 antibodies <sup>2</sup>	41 (70.7)
ELISA value (mean $\pm$ SD)	115.7 $\pm$ 85.5 UA/ml
Gliptin intake	
Vildagliptin	59 (54.6)
Sitagliptin	44 (40.7)
Saxagliptin	5 (4.6)
Associated treatments	
Metformin	68 (63.0)
Metformin+gliptin in single medication	46 (42.6)
Other antidiabetic treatments	31 (28.7)
Loop diuretic	22 (20.4)
Anti-aldosterone	5 (4.6)
Phenothiazine	1 (0.9)

3 <sup>1</sup> recorded in 98 patients

4 <sup>2</sup> performed in 58 patients

5

6

1 **Table 2. Comparison of the observed frequencies of gliptin intake (alone or in preparations associating metformin) in the Bullous**  
2 **Pemphigoid population with expected frequencies from indirect age standardization on a large sample (EGB sample) from the French**  
3 **general population.**

	Observed frequency of drug intake in the general population older than 50 years n; %	Expected frequency of drug intake in the BP population after age standardization on the French general population (EGB sample) n; %	Observed frequency of drug intake in the BP population n; % (95% CI)	Observed to expected drug intake frequency ratio (95% CI)	p value
<b>All gliptins</b>	8 729/225 412 ; 3.8 %	64.3/1 787 ; 3.6%	108/1 787 ; 6.0% (4.9-7.1%)	1.7 (1.4-2.0)	p <0.0001
<b>Sitagliptin</b>	5 698/225 412 ; 2.5%	44.1/1 787 ; 2.5%	44/1 787 ; 2.4% (1.7-3.2%)	1.0 (0.7-1.3)	p = 1
<b>Vildagliptin</b>	1 776/225 412 ; 0.8%	13.3/1 787 ; 0.7%	59/1 787 ; 3.3% (2.5-4.1%)	4.4 (3.5-5.7)	p <0.0001
<b>Saxagliptin</b>	890/225 412 ; 0.4%	1.2/1 787 ; 0.1%	5/1 787 ; 0.3% (0.0-0.7%) <sup>1</sup>	<sup>2</sup>	<sup>2</sup>
<b>All gliptins + metformin</b>	4 392/225 412 ; 1.9%	25.7/1 787 ; 1.4%	46/1 787 ; 2.6% (1.8-3.3%)	1.8 (1.3-2.4)	p <0.0001
<b>Sitagliptin+ metformin</b>	2 919/225 412 ; 1.3%	17.1/1 787 ; 1.0%	13/1 787 ; 0.7% (0.3-1.1%)	0.8 (0.4-1.3)	p = 0.33
<b>Vildagliptin+ metformin</b>	1 257/225 412 ; 0.6%	7.4/1 787 ; 0.4%	33/1 787 ; 1.9% (1.2-2.5%)	4.5 (3.2-6.3)	p <0.0001
<b>Saxagliptin+ metformin</b>	214/225 412 ; 0.09%	1.2/1 787 ; 0.1%	0/1 787 ; 0% (0.0-0.2%) <sup>1</sup>	<sup>2</sup>	<sup>2</sup>

4 CI: confidence interval ; <sup>1</sup> exact 95% Confidence interval ; <sup>2</sup> not calculated because there were too few exposed cases

1 **Table 3. Comparison of the delay of disease control, the rate and delay of relapse (in relapsing patients) of bullous pemphigoid patients**  
 2 **who used gliptins, depending on whether gliptin was stopped or continued.**

	Median delay of disease control (n=84)		p value <sup>1</sup>	Rate of relapse (n=74)		p value <sup>2</sup>	median delay of relapse (n=30)		p value <sup>1</sup>
	days (IQR)			n (%)			months (IQR)		
	Gliptin stopped	Gliptin continued	Gliptin stopped	Gliptin continued	Gliptin stopped	Gliptin continued			
<b>All gliptins</b>	15.0 (5.0-31.5)	14.0 (5.0-30.0)	0.95	17/39 (43.6)	13/35 (37.1)	0.63	4.8 (2.2-10.3)	5.8 (3.0-14.0)	0.90
<b>Sitagliptin</b>	17.5 (7.0-51.8)	14.0 (6.0-30.0)	0.77	8/15 (53.3)	5/14 (35.7)	0.34	6.7 (2.8-11.2)	5.8 (3.6-7.0)	0.94
<b>Vildagliptin</b>	10.0 (6.0-17.0)	15.0 (6.5-30.5)	0.29	7/21 (33.3)	9/20 (45.0)	0.44	3.0 (1.5-4.7)	6.0 (3.0-14.0)	0.29

3  
 4 IQR: interquartile range ; <sup>1</sup>Mann-Whitney's non parametric test ; <sup>2</sup>Pearson's chi-square test