Higher Frequency of Dipeptidyl Peptidase-4 Inhibitor Intake in Bullous Pemphigoid Patients than in the French General Population

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

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Short title: Gliptin-associated bullous pemphigoid

Abbreviations

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

Summary

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

INTRODUCTION

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

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

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

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

RESULTS

BP patients characteristics

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

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

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

and that of vildagliptin were higher than expected in BP patients (whole gliptin class: 6.0% (95% confidence interval (CI), 4.9-7.1%) versus 3.6%, p<0.0001); vildagliptin: 3.3% (95% CI, 2.5-4.1%) versus 0.7%, p<0.0001), corresponding to an observed to expected drug intake 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) for vildagliptin).

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

Clinical course of gliptin-associated BP depending on whether gliptin was continued or withdrawn

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

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

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

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

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

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

DISCUSSION

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

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

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

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

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

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

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

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

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

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

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

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

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

PATIENTS AND METHODS

Patients

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

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

Assessment of gliptin intake

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

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

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

Statistical analysis

Primary objective

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

Secondary objectives

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

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

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

CONFLICT OF INTEREST

The authors state no conflict of interest.

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

	n (%)
Gender	
Male	58 (53.7)
Female	50 (46.3)
Mean age ± SD (years)	77.9 ± 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 (≤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[1]	46 (46.9)
Anti-BP230 antibodies[2]	22 (37.9)
ELISA value (mean±SD)	43.2 ± 54.0 UA/ml
Anti-BP180 antibodies[2]	41 (70.7)
ELISA value (mean±SD)	115.7 ± 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)

[1] recorded in 98 patients

[2] performed in 58 patients

Table 2. Comparison of the observed frequencies of gliptin intake (alone or in preparations associating metformin) in the Bullous Pemphigoid population with expected frequencies from indirect age standardization on a large sample (EGB sample) from the French 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
All gliptins	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
Sitagliptin	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
Vildagliptin	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
Saxagliptin	890/225 412 ; 0.4%	1.2/1 787 ; 0.1%	5/1 787 ; 0.3% (0.0-0.7%)[1]	[2]	[2]
All gliptins + metformin	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
Sitagliptin+ metformin	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
Vildagliptin+ metformin	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
Saxagliptin+ metformin	214/225 412 ; 0.09%	1.2/1 787 ; 0.1%	0/1 787 ; 0% (0.0-0.2%)[1]	[2]	[2]

CI: confidence interval ; [1] exact 95% Confidence interval ; [2] not calculated because there were too few exposed cases

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

	Median delay of disease control (n=84) days (IQR)		p value[1]	Rate of relapse (n=74) n (%)		p value[2]	median delay of relapse (n=30) months (IQR)		p value[1]
	Gliptin stopped	Gliptin continued		Gliptin stopped	Gliptin continued		Gliptin stopped	Gliptin continued	
All gliptins	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
Sitagliptin	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
Vildagliptin	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

IQR: interquartile range ; [1]Mann-Whitney's non parametric test ; [2]Pearson's chi-square test