UNIL | Université de Lausanne
Faculté de biologie
et de médecine

Mémoire de Maîtrise en médecine

"Bullous pemphigoid induced by the dipeptidyl-peptidase IV inhibitors (gliptins)."

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Lausanne, janvier 2015

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Abstract

Background Bullous pemphigoid (BP) is the most frequent autoimmune blistering dermatosis. Recently, the development of BP in patients treated with gliptins, also known as DPP-4 inhibitors, alone or in association with metformin has been outlined in case reports. A possible mechanistic explanation that links gliptins with BP comes from the findings that DPP-4 inhibition enhances the activity of proinflammatory eotaxin chemokine and promotes eosinophil activation in the skin, which is known to contribute to blister formation in BP.

Objective To investigate a potential role of the gliptins in the development of BP in patients at the department of Dermatology of the University Hospital in Lausanne.

Methods We reviewed all patients with BP diagnosed at the University Hospital of Lausanne (CHUV) between January 2007 and July 2013 (n= 93). We assessed the causal relationship between BP development and the intake of gliptins for each patient according to the World Health Organization and Uppsala Monitoring Centre (WHO-UMC) scale, a standardised causality assessment scale of adverse drug reactions. We compared our results with the existing literature.

Results The yearly number of BP cases increased between 2007 and 2013. 23/93 BP patients had type 2 diabetes. The proportion of diabetic patients treated with gliptins in our study was 9/23 (39%) which is higher than the estimated proportion of patients treated with gliptins among the diabetic population (10-20%). In all nine cases, the causal relationship between drug intake and BP onset was classified as "possible", according to the WHO-UMC scale, which represents a probability less than 50% for BP to cause the disease.

Conclusion Our study shows a weak but possible correlation between gliptins intake and BP development. Thus gliptins may entertain the disease or unmask a subclinical disease in predisposed individuals. We must be aware of this potential dermatological side effect and have to evaluate diabetic patients to benefit from this drug with very good tolerability and few side effects. Studies on a larger scale are needed to further elucidate the mechanisms that would confirm the role of gliptins in the pathogenesis of bullous pemphigoid.

Keywords bullous pemphigoid, dipeptidyl-peptidase IV inhibitors, gliptins

Abbreviations: BP: bullous pemphigoid, CHUV: Centre Hospitalier Universitaire Vaudois, University Hospital of Lausanne, DIF: direct immunofluorescence, DPP-4: dipeptidyl-peptidase IV, GIP: glucose insulotropic peptide, GLP-1: glucagon-like peptide 1, IIF: indirect immunofluorescence, SSED-SGED: Société Suisse d'Endocrinologie et Diabétologie-Schweizerische Gesellschaft für Endokrinologie und Diabetologie.

1. Introduction

Bullous pemphigoid (BP) is the most frequent autoimmune blistering dermatosis. It is characterized by the synthesis of autoantibodies against two proteins, BP180 and BP230[1], also known as BPAG2 and BPAG1 respectively. Recently, the development of BP in patients treated with inhibitors of the dipeptidyl-peptidase IV (DPP-4/CD26) alone or in association with metformin has been outlined in case reports[2,3,4,5]. A possible mechanistic explanation that links gliptins with BP comes from the findings that DPP-4 inhibition enhances the activity of proinflammatory eotaxin chemokine[6] and promotes eosinophil activation in the skin, which is known to contribute to blister formation in BP[7,8].

Inhibitors of the DPP-4, known as gliptins, have been introduced in the oral treatment of type 2 diabetes in 2007 in Switzerland. Gliptins increase the secretion of insulin, through inhibition of the DPP-4 mediated catabolism of glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1)[9].

Due to the recent introduction of the DPP-4 inhibitors, their potential dermatological side effects have not been studied yet in the Swiss dermatological population. We investigated BP patients with diabetes in the department of Dermatology of the University Hospital (CHUV) in Lausanne since 2007 in order to identify a potential role of gliptins in the development of BP in this population.

2. Method

We conducted a clinical retrospective study. After a review of the literature we identified the patients diagnosed with BP in the department of Dermatology of the University Hospital in Lausanne between January 2007 and July 2013, thanks to the Diamic analysis system of the laboratory of pathology. The research system provided a list of all histopathological reports with the keyword «bullous pemphigoid» (n= 483). After selecting the cases where a BP diagnosis was retained (n= 93), we completed the search with the help of the clinical record to confirm that this diagnosis had been clinically retained, and to identify the cases that had type 2 diabetes (n= 23) treated with gliptins (n= 9). The files of the diabetic patients with BP were analyzed regarding: the diagnostic criteria reported for these cases: clinical, standard histological and immunofluorescence elements[10]; the antidiabetic treatment(s) received; the comorbidities and their treatments; the medical history of skin diseases. If a gliptin was mentioned in the medical record, we examined the chronology between BP diagnosis, treatment and onset and duration of the antidiabetic treatment(s). The missing data were

collected by contacting the concerned patients, their general practitioner and/or their chemist's. We assessed the causal relationship between BP development and the intake of gliptins for each patient according to the World Health Organization and Uppsala Monitoring Centre (WHO-UMC) scale[11]. It took into account the chronology between the suspect drug intake and the disease onset, reaction to drug discontinuation or rechallenge, plausibly involved concurrent drugs or diseases and supporting physiopathological evidence from the literature. The WHO-UMC scale does not give an accurate quantitative measurement of the correlation likelihood but classifies each case on a scale as "certain", "probable/likely", "possible", "unlikely" or "unclassified/unclassifiable". "Probable" and "possible" respectively correspond to a correlation likelihood of >50% and <50%. A statistical analysis was conducted, comparing the proportion of patients with BP and diabetes treated with gliptins to the proportion of the global diabetic population treated with gliptins. We also examined the evolution of the number of new cases diagnosed per year in the dermatological population of the University Hospital in Lausanne, to see whether there was a rise in the yearly number of BP cases with the increasing use of gliptins. Finally we compared our results with the existing literature.

3. Results

From January 2007 to July 2013, 93 patients were diagnosed with BP. Among these, 23 were diabetic and nine were treated with gliptins. The patients included in the study presented a clear diagnosis of BP based on typical diagnostic criteria: the clinical presentation, a matching lesion on the skin histopathology report and a positive direct immunofluorescence (DIF). In some cases, indirect immunofluorescence (IIF) and/or autoantibody (BP180 and BP230) dosage by ELISA confirmed the diagnosis. Patients developed BP between five months and four years after the introduction of the gliptin. In all nine cases, the causal relationship between drug intake and BP onset was classified as "possible", according to the WHO-UMC scale[11], which represents a probability less than 50% for BP to cause the disease. We describe each case's characteristics separately in Table 1.

The estimated proportion of diabetic patients treated with gliptins among the general diabetic population is 10 to 20% (source: department of Endocrinology, CHUV and Swiss society of endocrinology and diabetology (SSED-SGED)).

The distribution per year of the data we collected is listed in Table 2.

4. Discussion

In the Swiss population, BP has an incidence of 12.1 new cases per 1 million people per year and most cases arise without any identified etiology[12]. Chronic use of several drugs is known to be associated with the development of BP, especially spironolactone, phenothiazines[13,14] and recently gliptins. Drug-induced and idiopathic BP are indistinguishable clinically or histopathologically[3].

All our BP cases arose after the introduction of the gliptin treatment (with variable elapsed time), which is in favor of a causality relationship between the drug use and BP development. Drug-withdrawal was tested in two patients without significant improvement. One patient had a gliptin discontinued two years before he developed BP. Discontinuation of the gliptin was not tested for the six remaining patients. The antidiabetic medications of patients n°3 and n°5 were stopped on suspected drug-induced and gliptin-induced BP respectively. Even though patient n°3 had a quick favorable outcome without active lesion a few days after the interruption of his medication, a confounding factor is the rapid introduction of corticoids after the first symptoms. Therefore we cannot differentiate the respective influences of stopping the medication versus introducing an immunosuppressive therapy. Stable remission persisted despite reintroduction of the gliptin. This could be considered as a negative rechallenge. Regarding patient n°5, since there was no drastic change in the course of the disease after interruption of the gliptin, it is also difficult to assess its role in the pathogenesis of BP. He was already stable for a year on weekly methotrexate before the gliptin was stopped. The occasional pruritic symptoms of the patient are still present on methotrexate. It is also difficult to assess whether this mild pruritus is a residual BP symptom or a simple xerodermia with no specific pathophysiological mechanism implied.

Moreover, three patients (n°7, n°8 and n°9) showed sustained remission without BP treatment for respectively 6, 30 and 36 months even though they were still on gliptins, what speaks against a role of this medication in PB pathogenesis. None of our patients showed BP resistant to conventional immunosuppressive therapy. It is important to notice that none of the cases was classified as "unlikely", so we cannot exclude that gliptins are implicated in BP development. A confounding factor is that BP is a heterogeneous disease lasting from a few months to years. It has a frequent chronic course with spontaneous exacerbations and remissions[15]. Most patients achieve remission but relapses occur in almost 10% of the cases[16,17]. Gliptins might entertain BP in predisposed individuals, with very variable delay or unmask a subclinical disease. Even though the medication is maintained, it does not specifically promote relapses once the patient is cured.

An interesting fact to be noted is the type of gliptin incriminated in our study and in former reports. In the Skandalis and al. study, four patients were on vildagliptin plus metformin combination and one patient was on sitagliptin plus metformin combination. Three cases were classified as "possible" according to the WHO-UMC assessment scale and two (among the vildagliptin plus metformin group) as "probable/likely". In our study, five patients out of nine were on vildagliptin alone or in combination with metformin, three on sitagliptin alone or in combination with metformin and one on vildagliptin plus metformin later replaced by sitagliptin plus metformin combination. It is interesting to note that no other type of gliptin (alogliptin, linagliptin, saxagliptin) was involved in a suspect case of gliptin-induced BP, included in other case-reports[2,3,4,5]. Vildagliptin is the most frequently incriminated DPP-4 inhibitor. This may result from its popular use (it was the second gliptin to be approved by the American Food and Drug Administration in 2007 after sitagliptin[18]) or another yet unexplored mechanism due to its specific pharmacological properties.

The proportion of diabetic patients treated with gliptins in our study was 39% (9/23). This is significantly higher compared to the estimated proportion of diabetic patients treated with gliptins among the general diabetic population: 10 to 20% (source: department of Endocrinology, CHUV and the SSED-SGED). The large proportion of patients on gliptins in our study may be explained either by an implication of the gliptin, the advanced age and multiple comorbidities of the population studied, or a combination of these factors. Our population of patients had a mean age of 77.6 years, which is also the typical age of BP onset[12,14]. This older population has more comorbidities than the general population and may have less equilibrated diabetes requiring a 2nd-line treatment like a gliptin. In summary, more patients were treated with gliptins in the population studied than in the non-BP diabetic population of similar age, what is rather in favor of a gliptin-BP correlation.
In our study, 25% of the patients were diabetic, compared to the general population where the incidence of diabetes in patients over 75 years is approximately 18% in men and 8% in women[19]. Diabetes is thought to have a higher rate in BP patients than in the general population[20,21] and our results confirm this statement.

We observed an increasing number of BP in our population between 2007 and 2013 (Table 2). This might be explained by an increase in the incidence of BP due to the ageing of the general population or by improved diagnostic performances[22]. A bias to be considered is that we only reported the patients biopsied and diagnosed at the CHUV, and a referral bias cannot be excluded. The increasing use of gliptins over the years may also be involved. It is interesting to note this evolution but the population studied is not large enough to make any

conclusion.

Apart from clinical case reports about possibly gliptin-induced cases[2,3,4,5], dermatological adverse reactions described as blistering-necrotic skin lesions were reported in monkeys during gliptins preclinical trials[23]. We did not consider a potential role of metformin in BP onset because there is no report of any adverse skin reaction due to metformin in the literature. Gliptins themselves do not seem to interact with other drugs by modifying their pharmacokinetic profile, except for saxagliptin, which is metabolized in the liver to an active metabolite by CYP3A4/5[24].

Different physiopathological mechanisms could support a link between gliptins and the development of BP. DPP-4 has several functions as a regulatory protease involved in the digestion of cytokines, chemokines and growth factors, a binding protein for extracellular matrix components like collagen I and III, a costimulatory molecule for lymphocytes (T regulatory and T helper lymphocytes) and a receptor associated with CD45, an antigen expressed on all leucocytes[25]. The drug may act as a BP trigger by inhibiting the usual DPP-4 enzymatic function that reduces the proinflammatory activity of chemokines, as eotaxin[26] and thus promoting eosinophil activation in the skin[27], which is known to contribute to blister formation in BP[28, 29].

By contrast, other studies suggest that DPP-4 inhibitors could even protect from autoimmune diseases[30,31,]. In fact, the level of DPP-4 was found to correlate with the severity of some autoimmune diseases[32] and a decreased level of DPP-4 induces a rise in anti-inflammatory TGFβ secretion from T cells[30]. These different theories show that the precise mechanisms that link gliptins to the development of BP are not fully elucidated yet.

5. Conclusion

This is the first study to investigate the potential dermatological side effects of gliptins in the Swiss population. We reviewed the BP patients biopsied at the University Hospital of Lausanne for the past 6 years. This selection process did not include the patients biopsied before consulting at the University Hospital and the patients seen in private practice dermatologists. We cannot assess whether our results are representative of the whole BP population.

Although diagnostic delay in BP is thought to have no impact on prognosis[33], its morbidity has an impact on the quality of life of the patients. Our study shows a weak but possible relationship between gliptins intake and BP development. It confirms that we must be aware of gliptins' potential side effects and detect, investigate and treat a potential skin reaction early, without preventing diabetic patients to benefit from a drug with very good tolerability and few side effects compared to other antidiabetic medications[34]. Studies on a larger scale

are needed to further elucidate the mechanisms that would confirm the role of gliptins in the pathogenesis of bullous pemphigoid.

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Appendix

Table 1. BP in type-2 diabetes patients treated with DPP-4 inhibitors.

Patient No./Gender/ Age at BP onset [years]	Gliptin type	Gliptin present at BP onset [yes/no]	Period of gliptin use before BP onset [months]	BP outcome	Gliptin present at last follow-up [yes/no]	Relevant comorbidities and concurrent treatments[9,10,11]	Level of causality of drug-induction of BP[8]
1/M/70	Vildagliptin[A] Vildagliptin/Metformin[B] Saxagliptin/Metformin	Yes	**12**	Asymptomatic on MTX 10 mg/w at 6m follow-up	Yes	-	Possible
2/F/84	Sitagliptin/Metformin	Yes	**36**	Occasional pruritus on intermittent oral treatment (doxycycline, nicotinamide) at 8m follow-up.	Yes	-	Possible
3/M/73	Vildagliptin	Yes	**> 48**	Dermocorticoids withdrawal 7m after BP onset. Occasional pruritus since then at 1y follow-up.	Yes	-	Possible
4/F/70	Vildagliptin/Metformin	Yes	**5**	Dermocorticoids withdrawal 6m after BP onset. Relapsed course 7m later rapidly responsive to dermocorticoids. Occasional pruritus and bullae sensitive to dermocorticoids at 1.5y follow-up.	Yes	-	Possible
5/M/68	Vildagliptin[C] Sitagliptin/Metformin	Yes	**30**	Occasional pruritus on MTX 10 mg/w at 1.5y follow-up.	No. Stopped 11m after BP onset.	Dementia, seborrheic dermatitis.	Possible
6/M/80	Sitagliptin	No	**48**	Occasional pruritus on topical treatment (dermocorticoids 1x/w) at 2y follow-up.	No. Stopped 2y before BP onset.	-	Possible
7/M/85	Vildagliptin/Metformin	Yes	**> 48**	Dermocorticoids withdrawal 2.5y after BP onset. Asymptomatic since then at 6m follow-up.	Yes	Eczema (gluteal fold), spironolactone.	Possible
8/M/93	Vildagliptin	Yes	**21**	Dermocorticoids withdrawal ~2m after BP onset. Asymptomatic since then without treatment at 2.5y follow-up.	Yes	-	Possible
9/M/76	Sitagliptin	Yes	**10-11**	Dermocorticoids interrupted after 1y. Relapsed course 2y later. Dermocorticoids withdrawal 4m after relapse. Asymptomatic since then at 3y follow-up.	Yes	Recent apparition of cognitive impairment.	Possible

[A] switched for vildagliptin/metformin after 6m.
[B] switched for saxagliptin/metformin after 7m.
[C] switched for sitagliptin/metformin after 31m.
BP: bullous pemphigoid, F: female, M: male, MTX: methotrexate, m: month(s), w: week(s), y: year(s)

Table 2. Yearly number of BP cases from 2007 to July 2013.

	BP cases	BP patients with diabetes	BP patients with diabetes treated with a gliptin
2007	20	3	0
2008	8	1	0
2009	9	1	0
2010	13	3	1
2011	13	4	2
2012	18	6	3
2013 (→ July)	12	5	3
Total	**93**	**23**	**9**