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Use of Dipeptidyl-Peptidase IV Inhibitors and Bullous Pemphigoid

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An increasing number of reports suggest that inhibitors of the dipeptidyl-peptidase IV (DPP4i) are implicated in the development of bullous pemphigoid (BP) [1–8]. We investigated BP patients diagnosed in our center (Department of Dermatology and Venereology, Lausanne University Hospital Centre) between January 2007, the year in which the first DPP4i was introduced in Switzerland, and July 2013 to assess whether the use of DPP4i in diabetic patients is potentially related to the development of BP. We searched the database of the laboratory of dermatopathology with the keyword "bullous pemphigoid" between January 2007 and July 2013. We next identified patients with a definite diagnosis of BP with or without adult onset diabetes mellitus (AODM). The diagnosis of BP was based on typical or consistent clinical features, typical or compatible histological findings, and positive immunopathological studies, including direct and indirect immunofluorescence microscopy, and enzyme-linked immunosorbent assays (ELISA) for BP180 and BP230 [9]. If serum was not available for testing, diagnosis was based on the presence of 3 of 4 well-established clinical criteria for BP in patients having linear deposits of C3 and/or IgG along the epidermal basement membrane as detected by direct immunofluorescence microscopy: age >70 years and absence of atrophic scarring, mucosal involvement, and predominant bullous lesions on the neck and head [10].

The files of diabetic patients with BP were systematically analyzed with regard to (1) antidiabetic treatment(s); (2) comorbidities; (3) history of skin diseases; and (4) chronology between BP diagnosis, treatment, and onset and duration of the DPP4i treatment(s). The association between BP development and the intake of DPP4i for each patient was assessed according to the World Health Organization and Uppsala Monitoring Centre (WHO-UMC) scale, a standardized causality assessment scale of adverse drug reactions [11], to allow direct comparison with the aforementioned study [1].

The control group consisted of 170 patients with AODM, selected by year of birth, who were followed up by the endocrinology outpatient clinic between 2012 and 2014. The patients' files were reviewed concerning treatment for diabetes, specifically the use of DPP4i. Both groups were compared for gender, treatment with DPP4i, age, and calendar year of consultation with a 2-sample *t* test. The χ^2 test and the Wilcoxon rank-sum test were used for categorical and continuous variables, respectively. We compared exposure to DPP4i in both groups with adjustment for confounders such as age, gender, and calendar year of visit with multiple logistic regression models. Effect of exposure was expressed in terms of odds ratios (OR) along with their 95% confidence intervals (CI). Analyses were carried out with Stata software (version 13.1, 2014; StataCorp, College Station, TX, USA). All tests were considered statistically significant at $p < 0.05$.

Between January 2007 and July 2013, we identified 93 BP patients. Among these, 23 (24.7%; 12 women/11 men) were diabetic, 9 of whom were treated with DPP4i. The mean age at inclusion in the case series was 77.6 years (68–93 years). The average follow-up was 55.3 months (32–73 months) (Table 1). Patients developed BP between 5 months and over 4 years after the introduction of DPP4i. Of the 9 patients, 5 were on vildagliptin ± metformin, 3 were on sitagliptin ± metformin, and 1 was on vildagliptin/metformin (later replaced by sitagliptin/metformin) combination. In 7 cases, the association between drug intake and BP onset was classified as "possible," which represents a probability of less than 50% for DPP4i to have caused the disease. Two cases (patients 3 and 7) developed BP more than 48 months after the first use of DPP4i and were classified as unlikely.

A total of 170 nondermatological control patients (57 women/113 men) were selected, with a mean age of 76.5 years. Use of DPP4i was found in 9 out of 23 (39.1%) BP patients with AODM and in 57 out of 170 (33.5%) diabetic control patients. The crude OR for DPP4i use in diabetic BP patients was 1.27 (95% CI, 0.52–3.12, $p = 0.596$). When the effect of gender, age, and calendar year was accounted for, the adjusted OR increased to 2.48 (95% CI, 0.75–8.3, $p = 0.137$).

An increasing number of patients who developed BP during treatment with DPP4i has been reported, raising the question about a causal relationship [3–10]. In France, there has been an average of 10 cases of possible DPP4i-induced BP cases per year from 2008 to 2012 [12, 13].

We observed a prevalence of 39% of DPP4i in cases and 33% in controls. When the effect of gender, age, and year was accounted for, there was a nonsignificant trend towards more use of DPP4i in BP patients. Most diabetic patients with BP had a history of vildagliptin use, a molecule already incriminated in a previous study [1].

A total of 24.7% of the BP patients were diabetic, with a similar proportion of women and men (25 and 24.4% respectively), whereas in the general Swiss population aged 75 years or older, the prev-

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Table 1. Demographics and characteristics of the BP cases with type-2 diabetes treated with DPP-4 inhibitors

Patient/ gender/ age, years	Gliptin type	Gliptin at onset (yes/no)	Gliptin intake prior to BP onset, months	BP outcome	Gliptin at last follow-up (yes/no)	Comorbidities/other therapies [9–11]	Causality drug induction [8]
1/M/70	Vildagliptin[a] Saxagliptin/metformin[b] Vildagliptin[c] Sitagliptin/metformin	Yes	12	Relapse at 39 months after the initial episode, currently on MTX 15 mg/week 45 months of follow-up	Yes	–	Possible
2/F/84	Sitagliptin/metformin	Yes	36	Remission after doxycycline and nicotinamide Occasional itch 48 months of follow-up	No	–	Possible
3/M/73	Vildagliptin	Yes	>48	Remission after topical corticosteroids 52 months of follow-up	No	–	Unlikely
4/F/70	Vildagliptin/metformin	Yes	5	Last relapse at 78 months after the initial episode, 3 relapses in total treated with topical corticosteroid courses 45 months of follow-up	Yes	–	Possible
5/M/68	Vildagliptin[d] Sitagliptin/metformin	Yes	30	Remission on MTX 10 mg/week and dermocorticoids 32 months of follow-up	No	Dementia	Possible
6/M/80	Sitagliptin	No, stopped 24 months before	48	Remission after topical corticosteroids Occasional itch 63 months of follow-up	No	–	Possible
7/M/85	Vildagliptin/metformin	Yes	>48	Remission after topical corticosteroids 68 months of follow-up	Yes	Spironolactone intake	Unlikely
8/M/93	Vildagliptin	Yes	21	Remission after topical corticosteroids 72 months of follow-up	Yes	–	Possible
9/M/76	Sitagliptin	Yes	10–11	Remission after topical corticosteroid courses with relapse 73 months of follow-up	Yes	Dementia	Possible

BP, bullous pemphigoid; F, female; M, male; MTX, methotrexate. [a] Switched to saxagliptin/metformin after 36 months. [b] Switched to vildagliptin again after 24 months. [c] Switched to sitagliptin/metformin after 14 months. [d] Switched to sitagliptin/metformin after 31 months.

alence of AODM is approximately 15% in men and 11% in women [14]. Our findings support previous reports suggesting an association between AODM and BP [15, 16].

This is the first study to investigate the potential role of DPP4i in triggering BP in the Swiss population. Based on the available data, an association between the onset of BP and the use of DPP4i cannot be shown. Further prospective studies are needed to validate our findings.

Key Message

Our retrospective case-control study raises the awareness that BP might be a potential side effect of DPP4i.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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