Vildagliptin significantly increases the risk of bullous pemphigoid: A Finnish nationwide registry study

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Abbreviations: ATC: Anatomical Therapeutic Chemical; ADR: adverse drug reaction; BCC: Basocellular carcinoma; BP: bullous pemphigoid; CI: confidence interval; DPP-4i: Dipeptidyl peptidase-4 inhibitor; ICD: International Classification of Diseases; OR: odds ratio

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Bullous pemphigoid (BP) is the most common autoimmune blistering skin disease (Schmidt and Zillikens, 2013). BP has become more common over the past two decades (Langan et al, 2008, Joly et al, 2012, Forsti et al, 2014). However, the underlying causes of the increasing incidence of BP are poorly understood. Altogether, over 50 drugs have been reported to induce BP (Stavropoulos, Soura and Antoniou, 2014). The use of dipeptidyl peptidase-4 inhibitors (DPP-4i), a class of drug used for the treatment of diabetes, has recently been scrutinized as a risk factor for BP, both in case reports (Table S1) and in national pharmacovigilance database reports (Bene et al, 2016, García et al, 2016), but large population-based studies are lacking. In the present study we investigated the potential association between DPP-4i and BP using data from Finnish national registries.

Populations, databases used and statistical analysis are described in Supplementary materials. After adjusting for diabetes and several neurological disorders, the use of any DPP-4i was associated with a significantly increased risk of BP compared with the control population. The use of vildagliptin was associated with ten-fold elevated risk for BP. Combination therapy regimens containing metformin and sitagliptin or vildagliptin were associated with an increased risk of BP, but metformin alone was not associated with a difference in BP risk. A sensitivity analysis supported these findings. (Table 2, S2) The use of DPP-4i had no significant impact on patient age at BP diagnosis, when subjects who had received a DPP-4i were compared with those who had not (77.7 vs. 76.7 years) starting from 2007 when the first DPP-4 inhibitor was approved in Finland. The mean latency from vildagliptin exposure to BP diagnosis was 449 days (Table S3). In women, the risk of having BP diagnosis after DPP-4i medication was heightened compared to men (Table S4).

To the best of our knowledge, no previous nationwide registry study has reported an association between vildagliptin and BP. These results concur with previous observations from pharmacovigilance database reports where BP was most frequent with vildagliptin therapy.

(Bene et al, 2016, García et al, 2016). Furthermore, freely available information from the European database of suspected adverse drug reaction (ADR) supports our findings: by December 2017, 408 vildagliptin-associated suspected pemphigoid cases (of a total of 3653 ADRs) were recorded in this database whereas there were notably fewer pemphigoid cases linked to sitagliptin (173 of the total of 12439 ADRs) (www.adrreports.eu). Our results are also in line with those of recent studies reporting elevated risk for BP associated with vildagliptin use (Benzaquen et al, 2017, Schaffer et al, 2017).

From the year 2011, an increasing number of case reports have been published linking DPP-4i and BP (Table S1). Most concern vildagliptin, but some cases have also been reported during linagliptin, sitagliptin, anagliptin and alogliptin therapy. The latency period between DPP-4i use and the onset of BP in these reports ranges between one month and over four years (Table S1) and in recent pharmacovigilance reports the mean latency period varied from 6 to 19 months (García et al, 2016, Bene et al, 2016). In our study the mean time between vildagliptin intake and BP diagnosis was 449 days. Thus, vildagliptin should be recognized as a possible trigger for BP even when it has been used for more than a year before BP diagnosis. It is noteworthy that metformin monotherapy was not associated with BP when adjusted for diabetes and neurological diseases. This implies that in BP cases diagnosed during metformin-vildagliptin combination therapy, metformin could be safely continued while withdrawal of vildagliptin should be considered. It is currently unclear whether DPP-4i-associated BP is an actual drug-induced BP, which truly resolves upon cessation of the drug, or rather a drug-aggravated BP, which persists despite the cessation of the drug.

An interesting finding in our study was that women were more likely than men to develop BP after DPP-4i intake (Table S4). In the European pharmacovigilance report, 58% of vildagliptin, 65% of sitagliptin, 46% of linagliptin and 33% of saxagliptin related BP cases were men (García et al, 2016) while in a recent case-control study the risk of BP onset after DPP-4i therapy was

only seen in males (Benzaquen et al, 2017). In healthy persons, gender does not affect the pharmacokinetics of vildagliptin (He et al, 2008), but women are known to be in increased risk of adverse drug reactions in general (Rademaker, 2001). However, further studies are needed to verify the differences between genders in susceptibility for BP onset during DPP-4i therapy.

As well as BP, vildagliptin and sitagliptin have been reported to induce polyarthritis (Saito et al, 2013, Crickx et al, 2014). DPP-4i have also been suggested to decrease the risk of autoimmune diseases: in a cohort study of a U.S. insurance database the use of linagliptin, saxagliptin or sitagliptin slightly reduced the risk of rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, psoriasis and inflammatory bowel disease, but the risk of autoimmune blistering skin diseases was not analyzed in this study (Kim et al, 2015). Taken together, currently only limited data are available concerning the association of DPP-4i with other autoimmune diseases.

A major strength of our study is that the data from the Social Insurance Institution of Finland contain information on medication that patients have actually purchased. Another strength is that it utilized one of the largest nationwide BP cohorts ever studied (Försti et al, 2017). Due to the use of routinely collected registry data we have no certainty that all the BP cases were immunologically confirmed and no access to information of the actual onset of the BP symptoms. It was not possible to analyze any relationship between linagliptin or saxagliptin and BP due to few patients using these medications. The use of patients with BCC as a control population may have introduced some confounding factors: compared with age- and sex-matched BCC controls, BP patients are more likely to have diabetes and their diabetes may be more severe. In the future, it is important to investigate the association between the use of DPP-4i and BP by comparing the incidence of BP in patients treated for diabetes with DPP-4i and those treated with other diabetes medications.

In conclusion, our nationwide registry study demonstrates a significantly increased risk of BP following the use of vildagliptin. Further studies are required better to understand the pathomechanism that causes the association between DPP-4i and BP.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Table 1. Characteristics of bullous pemphigoid cases and basocellular carcinoma controls from the Finnish Care Register for Heath Care

	Cases n = 3397 (%)	Controls n = 12941 (%)[1]
Female	2028 (59.7)	7766 (60.0)
Male	1369 (40.3)	5175 (40.0)
Age years mean	76.6	76.7
Diabetes	757 (22.3)	1837 (14.2)
Neurological disease[2]	1519 (44.7)	3949 (30.5)

[1] Age, sex and year of the diagnosis matched in 1:4 ratio. Due to availability of drug reimbursement data, 579 patients had fewer than 4 basocellular carcinoma controls.

[2] Alzheimer's disease, vascular dementia, other/unspecified dementia, Parkinson's disease, multiple sclerosis, subarachnoid hemorrhage, intracerebral hemorrhage, cerebral infarction and epilepsy

Table 2. Metformin and dipeptidyl peptidase 4 inhibitor drugs used by bullous pemphigoid cases and basocellular carcinoma controls obtained from the database of the Social Insurance Institution of Finland and Odds Ratios for bullous pemphigoid

Drug	Group	Total [1]	N (%)	Crude OR (95% CI)	Adjusted OR (95% CI)[2]	Adjusted OR (95% CI)[3]
Combinations of oral blood glucose lowering drugs						
Metformin and sitagliptin	Cases	1621	27 (1.7)	3.95 (2.30 - 6.78)	2.34 (1.20 - 4.57)	2.40 (1.22 - 4.73)
	Controls	6411	29 (0.5)	Reference	Reference	Reference
Metformin and vildagliptin	Cases	1777	14 (0.8)	6.59 (2.75 - 15.8)	4.21 (1.59 - 11.10)	6.71 (2.00 - 22.50)
	Controls	6989	9 (0.1)	Reference	Reference	Reference
Dipeptidyl peptidase 4 (DPP-4) inhibitors	Cases	1917	124 (6.5)	3.45 (2.69 - 4.44)	2.13 (1.51 - 3.00)	2.19 (1.55 - 3.11)
	Controls	7536	153 (2.0)	Reference	Reference	Reference
Sitagliptin	Cases	1917	79 (4.1)	2.37 (1.78 - 3.17)	1.36 (0.93 - 1.99)	1.37 (0.93 - 2.01)
	Controls	7536	135 (1.8)	Reference	Reference	Reference
Vildagliptin	Cases	1807	49 (2.7)	11.8 (6.71 - 20.8)	8.66 (4.06 - 18.50)	10.4 (4.56 - 23.80)
	Controls	7152	17 (0.2)	Reference	Reference	Reference
Saxagliptin	Cases	1295	1 (0.1)			
	Controls	5157	2 (0.0)			
Linagliptin	Cases	848	2 (0.2)			
	Controls	3488	1 (0.0)			
Biguanides						
Metformin	Cases	3397	432 (12.7)	1.49 (1.32 - 1.68)	1.00 (0.84 - 1.18)	1.05 (0.88 - 1.24)
	Controls	12941	1178 (9.1)	Reference	Reference	Reference

[1] Including cases and controls diagnosed after the drug in question had been approved for use in Finland
[2] OR adjusted for diabetes
[3] OR adjusted for diabetes, Alzheimer's disease, vascular dementia, other/unspecified dementia, Parkinson's disease, multiple sclerosis, subarachnoid hemorrhage, intracerebral hemorrhage, cerebral infarction and epilepsy.