REFERENCES

Chaturvedi RK, Flint Beal M. Mitochondrial diseases of the brain. Free Radic Biol Med 2013;63:1–29.

Dozsa A, Mihaly J, Dezso B, Csizmadia E, Keresztessy T, Marko L, et al. Decreased peroxisome proliferator-activated receptor gamma level and signalling in sebaceous glands of patients with acne vulgaris. Clin Exp Dermatol 2016;41:547–51.

Hock MB, Kralli A. Transcriptional control of mitochondrial biogenesis and function. Annu Rev Physiol 2009;71:177–203.

Kloepper JE, Baris OR, Reuter K, Kobayashi K, Weiland D, Vidali S, et al. Mitochondrial function in murine skin epithelium is crucial for hair follicle morphogenesis and epithelial-mesenchymal interactions. J Invest Dermatol 2015;135:679–89.

Knuever J, Poeggeler B, Gaspar E, Klinger M, Hellwig-Burgel T, Hardenbicker C, et al. Thyrotropin-releasing hormone controls mitochondrial biology in human epidermis. J Clin Endocrinol Metab 2012;97:978–86.

Langan EA, Philpott MP, Kloepper JE, Paus R. Human hair follicle organ culture: theory, application and perspectives. Exp Dermatol 2015;24:903–11.

Philpott MP, Kealey T. Metabolic studies on isolated hair follicles: Hair follicles engaged in aerobic glycolysis and do not demonstrate the glucose fatty acid cycle. J Invest Dermatol 1990;96:875–9.

Ramot Y, Mastrofrancesco A, Camera E, Desreumaux P, Paus R, Picardo M. The role of PPARgamma-mediated signalling in skin biology and pathology: new targets and opportunities for clinical dermatology. Exp Dermatol 2015;24:245–51.

Ramot Y, Mastrofrancesco A, Herczeg-Lisztes E, Biro T, Picardo M, Kloepper JE, et al. Advanced inhibition of undesired human hair growth by PPARgamma modulation? J Invest Dermatol 2014;134:1128–31.

Ramot Y, Tiede S, Biro T, Abu Bakar MH, Sugawara K, Philpott MP, et al. Spermidine promotes human hair growth and is a novel modulator of human epithelial stem cell functions. PLoS One 2011;6:e22564.

Ruzehaji N, Frantz C, Ponsoye M, Avouac J, Pezet S, Guilbert T, et al. Pan PPAR agonist IVA337 is effective in prevention and treatment of experimental skin fibrosis. Ann Rheum Dis 2016;75:2175–83.

Sertznig P, Seifert M, Tilgen W, Reichrath J. Peroxisome proliferator-activated receptors (PPARs) and the human skin: importance of PPARs in skin physiology and dermatologic diseases. Am J Clin Dermatol 2008;9:15–31.

Sorgato M, Moran O. Channels in mitochondrial membranes: knowns, unknowns, and prospects for the future. Crit Rev Biochem Mol Biol 1933;18:127–71.

Vidali S, Chéret J, Giesen M, Haeger S, Alam M, Watson REB, et al. Thyroid hormones enhance mitochondrial function in human epidermis. J Invest Dermatol 2016;136:2003–12.

Vidali S, Knuever J, Lerchner J, Giesen M, Biro T, Klinger M, et al. Hypothalamic-pituitary-thyroid axis hormones stimulate mitochondrial function and biogenesis in human hair follicles. J Invest Dermatol 2014;134:33–42.

Wallmeyer L, Lehnen D, Eger N, Sochorova M, Opalka L, Kovacik A, et al. Stimulation of PPARalpha normalizes the skin lipid ratio and improves the skin barrier of normal and filaggrin deficient reconstructed skin. J Dermatol Sci 2015;80:102–10.

Williams R, Philpott MP, Kealey T. Metabolism of freshly isolated human hair follicles capable of hair elongation: a glutaminolytic, aerobic glycolytic tissue. J Invest Dermatol 1993;100:834–40.

Yin K, Smith AG. Nuclear receptor function in skin health and disease: therapeutic opportunities in the orphan and adopted receptor classes. Cell Mol Life Sci 2016;73:3789–800.

Vildagliptin Significantly Increases the Risk of Bullous Pemphigoid: A Finnish Nationwide Registry Study

Journal of Investigative Dermatology (2018) **138,** 1659–1661; doi:10.1016/j.jid.2018.01.027

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 (Försti et al., 2014; Joly et al., 2012; Langan et al., 2008). However, the underlying causes of the increasing incidence of BP are poorly understood. Altogether, over 50 drugs have been reported to induce BP (Stavropoulos et al., 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 (see Supplementary Table S1 online) and in national pharmacovigilance database reports (Bene et al., 2016; García et al., 2016), but large population-based studies are lacking. In this study we investigated the potential association between DPP-4i and BP using data from Finnish national registries.

Populations (Table 1), databases used, and statistical analysis are described in the Supplementary Materials online. 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 (Table 2). The use of vildagliptin was associated with 10-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, and see Supplementary Table S2 online). 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-4i was approved in Finland. The mean latency from vildagliptin exposure to BP diagnosis was 449 days (see Supplementary Table S3 online). In women, the risk of having BP diagnosis after DPP-4i medication was heightened compared with men (see Supplementary Table S4 online).

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

Abbreviations: BP, bullous pemphigoid; DPP-4i, dipeptidyl peptidase-4 inhibitor

Accepted manuscript published online 7 February 2018; corrected proof published online 14 March 2018

Table 1. Characteristics of bullous pemphigoid patients and basal cell carcinoma control individuals from the Finnish Care Register for Heath Care

Characteristic	Patients (n = 3,397)	Control Individuals (n = 12,941)[1]
Female, n (%)	2,028 (59.7)	7,766 (60.0)
Male, n (%)	1,369 (40.3)	5,175 (40.0)
Age in years, mean	76.6	76.7
Diabetes, n (%)	757 (22.3)	1,837 (14.2)
Neurological disease, n (%)[2]	1,519 (44.7)	3,949 (30.5)

[1]Age, sex, and year of the diagnosis matched in 1:4 ratio. Because of the availability of drug reimbursement data, 579 patients had fewer than four basal cell carcinoma control individuals.
[2]Alzheimer disease, vascular dementia, other/unspecified dementia, Parkinson disease, multiple sclerosis, subarachnoid hemorrhage, intracerebral hemorrhage, cerebral infarction, and epilepsy.

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 supports our findings: by December 2017, 408 vildagliptin-associated suspected pemphigoid cases (of a total of 3,653 adverse drug reactions) were recorded in this database, whereas there were notably fewer pemphigoid cases linked to sitagliptin (173 of the total of 12,439 adverse drug reactions) (European Medicines Agency, n.d.). 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 (see Supplementary 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 1 month and over 4 years (see Supplementary Table S1), and in recent pharmacovigilance reports the mean latency period varied from 6 to 19 months (Bene et al., 2016; García 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. Metformin monotherapy was not associated with BP when adjusted for diabetes and neurological diseases. This implies that for patients with BP diagnosed during metformin-vildagliptin combination therapy, metformin could be safely continued, but 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 cessation of the drug.

Table 2. Metformin and dipeptidyl peptidase-4 inhibitor drugs used by bullous pemphigoid patients and basal cell carcinoma control individuals 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	Patients	1,621	27 (1.7)	3.95 (2.30–6.78)	2.34 (1.20–4.57)	2.40 (1.22–4.73)
	Control individuals	6,411	29 (0.5)	Reference	Reference	Reference
Metformin and vildagliptin	Patients	1,777	14 (0.8)	6.59 (2.75–15.8)	4.21 (1.59–11.10)	6.71 (2.00–22.50)
	Control individuals	6,989	9 (0.1)	Reference	Reference	Reference
Dipeptidyl peptidase-4 inhibitors	Patients	1,917	124 (6.5)	3.45 (2.69–4.44)	2.13 (1.51–3.00)	2.19 (1.55–3.11)
	Control individuals	7,536	153 (2.0)	Reference	Reference	Reference
Sitagliptin	Patients	1,917	79 (4.1)	2.37 (1.78–3.17)	1.36 (0.93–1.99)	1.37 (0.93–2.01)
	Control individuals	7,536	135 (1.8)	Reference	Reference	Reference
Vildagliptin	Patients	1,807	49 (2.7)	11.8 (6.71–20.8)	8.66 (4.06–18.50)	10.4 (4.56–23.80)
	Control individuals	7,152	17 (0.2)	Reference	Reference	Reference
Saxagliptin	Patients	1,295	1 (0.1)	—	—	—
	Control individuals	5,157	2 (0.0)	—	—	—
Linagliptin	Patients	848	2 (0.2)	—	—	—
	Control individuals	3,488	1 (0.0)	—	—	—
Biguanides						
Metformin	Patients	3,397	432 (12.7)	1.49 (1.32–1.68)	1.00 (0.84–1.18)	1.05 (0.88–1.24)
	Control individuals	12,941	1,178 (9.1)	Reference	Reference	Reference

Abbreviations: CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitor; OR, odds ratio.
[1]Including patients and control individuals with disease diagnosed after the drug in question had been approved for use in Finland.
[2]OR adjusted for diabetes.
[3]OR adjusted for diabetes, Alzheimer disease, vascular dementia, other/unspecified dementia, Parkinson disease, multiple sclerosis, subarachnoid hemorrhage, intracerebral hemorrhage, cerebral infarction, and epilepsy.

An interesting finding in our study was that women were more likely than men to develop BP after DPP-4i intake (see Supplementary Table S4). In the European pharmacovigilance report, 58% of vildagliptin-, 65% of sitagliptin-, 46% of linagliptin-, and 33% of saxagliptin-related BP patients were men (García et al., 2016), and 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, sex does not affect the pharmacokinetics of vildagliptin (He et al., 2008), but women are known to be at increased risk for adverse drug reactions in general (Rademaker, 2001). However, further studies are needed to verify the differences between sexes in susceptibility for BP onset during DPP-4i therapy.

As well as BP, vildagliptin and sitagliptin have been reported to induce polyarthritis (Crickx et al., 2014; Saito et al., 2013). DPP-4i have also been suggested to decrease the risk of autoimmune diseases: in a cohort study of a US 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 we used one of the largest nationwide BP cohorts ever studied (Försti et al., 2017). Because of 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 because few patients used these medications. The use of patients with basal cell carcinoma as a control population may have introduced some confounding factors: compared with age- and sex-matched basal cell carcinoma control individuals, BP patients are more likely to have diabetes, and their diabetes may be more severe. In the future, it will be 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 shows a significantly increased risk of BP after 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 state no conflict of interest.

ACKNOWLEDGMENTS

This study was supported by research grants from the Academy of Finland and the Medical Research Center Oulu.

Outi Varpuluoma[1,2], Anna-Kaisa Försti[1,2], Jari Jokelainen[3,4], Miia Turpeinen[5,6], Markku Timonen[4], Laura Huilaja[1,2] and Kaisa Tasanen[1,2,*]

[1]PEDEGO Research Unit, University of Oulu, Oulu, Finland; [2]Department of Dermatology and Medical Research Center Oulu, Oulu University Hospital, Oulu, Finland; [3]Unit of General Practice, Oulu University Hospital, Oulu, Finland; [4]Center for Life Course Epidemiology and Systems Medicine, University of Oulu, Oulu, Finland; [5]Administration Center and Medical Research Center Oulu, Oulu University Hospital, Oulu, Finland; and [6]Research Unit of Biomedicine, University of Oulu, Oulu, Finland

[*]Corresponding author e-mail: kaisa.tasanen@oulu.fi

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2018.01.027.

REFERENCES

Bene J, Moulis G, Bennani I, Auffret M, Coupe P, Babai S, et al. Bullous pemphigoid and dipeptidyl peptidase IV inhibitors: A case-noncase study in the french pharmacovigilance database. Br J Dermatol 2016;175:296–301.

Benzaquen M, Borradori L, Berbis P, Cazzaniga S, Valero R, Richard M, et al. Dipeptidyl peptidase-IV inhibitors, a risk factor for bullous pemphigoid. Retrospective multicenter case-control study in France and Switzerland [e-pub ahead of print]. J Am Acad Dermatol 2017; https://doi.org/10.1016/j.jaad.2017.12.038 (accessed 20 December 2017).

Crickx E, Marroun I, Veyrie C, Le Beller C, Schoindre Y, Bouilloud F, et al. DPP4 inhibitor-induced polyarthritis: a report of three cases. Rheumatol Int 2014;34:291–2.

European Medicines Agency. EudraVigilance, http://www.adrreports.eu; n.d. (accessed 20 January 2018).

Försti AK, Jokelainen J, Timonen M, Tasanen K. Increasing incidence of bullous pemphigoid in northern Finland: a retrospective database study in Oulu University Hospital. Br J Dermatol 2014;171:1223–6.

Försti AK, Huilaja L, Schmidt E, Tasanen K. Neurological and psychiatric associations in bullous pemphigoid—more than skin deep? Exp Dermatol 2017;26:1228–34.

García M, Aranburu MA, Palacios-Zabalza I, Lertxundi U, Aguirre C. Dipeptidyl peptidase-IV inhibitors induced bullous pemphigoid: a case report and analysis of cases reported in the European pharmacovigilance database. J Clin Pharm Ther 2016;41:368–70.

He Y, Sabo R, Campestrini J, Wang Y, Riviere G, Nielsen JC, et al. The effect of age, gender, and body mass index on the pharmacokinetics and pharmacodynamics of vildagliptin in healthy volunteers. Br J Clin Pharmacol 2008;65:338–46.

Joly P, Baricault S, Sparsa A, Bernard P, Bedane C, Duvert-Lehembre S, et al. Incidence and mortality of bullous pemphigoid in France. J Invest Dermatol 2012;132:1998–2004.

Kim SC, Schneeweiss S, Glynn RJ, Doherty M, Goldfine AB, Solomon DH. Dipeptidyl peptidase-4 inhibitors in type 2 diabetes may reduce the risk of autoimmune diseases: a population-based cohort study. Ann Rheum Dis 2015;74:1968–75.

Langan SM, Smeeth L, Hubbard R, Fleming KM, Smith CJP, West J. Bullous pemphigoid and pemphigus vulgaris—incidence and mortality in the UK: population based cohort study. BMJ 2008;337:a180.

Rademaker M. Do women have more adverse drug reactions? Am J Clin Dermatol 2001;2:349–51.

Saito T, Ohnuma K, Suzuki H, Dang NH, Hatano R, Ninomiya H, et al. Polyarthropathy in type 2 diabetes patients treated with DPP4 inhibitors. Diabetes Res Clin Pract 2013;102:e12.

Schaffer C, Buclin T, Jornayvaz FR, Cazzaniga S, Borradori L, Gilliet M, et al. Use of dipeptidyl-peptidase IV inhibitors and bullous pemphigoid. Dermatology 2017;233:401–3.

Schmidt E, Zillikens D. Pemphigoid diseases. Lancet 2013;381:320–32.

Stavropoulos PG, Soura E, Antoniou C. Drug-induced pemphigoid: a review of the literature. J Eur Acad Dermatol Venereol 2014;28:1133–40.