Bullous Pemphigoid and Dipeptidyl Peptidase 4 Inhibitors: A Disproportionality Analysis Based on the Japanese Adverse Drug Event Report Database

Masanori Arai, Jun Shirakawa, Hiromi Konishi, Naoko Sagawa, and Yasuo Terauchi

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Bullous pemphigoid (BP) is a rare autoimmune blistering skin disease. Although previous case reports and two disproportionality analyses of European populations have suggested associations between dipeptideyl peptidase 4 (DPP-4) inhibitor use and BP (1–3), the involvement of race, antidiabetes drugs, sex, age, and other risk factors in BP induced by DPP-4 inhibitors has not yet been evaluated. We conducted disproportionality analysis using the Japanese Adverse Drug Event Report (JADER) database, which contains all pharmacovigilance data that have been spontaneously reported to the Pharmaceuticals and Medical Devices Agency (PMDA) since April 2004.

As of June 2017, the database contained 454,027 reports of adverse drug reactions. For this study, data were downloaded from the PMDA website (http://www.pmda.go.jp). Potential signals of DPP-4 inhibitors or other drugs with BP were assessed with categories using the reporting odds ratio (ROR), which is an established parameter in pharmacovigilance research. An ROR was calculated using a two-by-two contingency table (4). We examined DPP-4 inhibitors (alogliptin, anagliptin, linagliptin, omarigliptin, saxagliptin, sitagliptin, trelagliptin, teneligliptin, and vildagliptin), other antihyperglycemia drug classes (sulfonylureas, biguanides, α-glucosidase inhibitors [α-GIs], glinides, glucagon-like peptide 1 receptor agonists [GLP-1 RAs], sodium–glucose cotransporter 2 inhibitors [SGLT2is], thiazolidines, and any kind of insulins), other drugs that are reported as causal reagents for BP, and negative controls (2,5). An ROR is considered significant when the lower bound of the two-sided 95% CI for the risk of BP was larger than 1. The data were analyzed using the R software (version 3.4.0; The R Foundation for Statistical Computing, Vienna, Austria).

In the database, 546 BP (referred to as pemphigoid in the database) case subjects were found. The total number of reports of BP associated with DPP-4 inhibitor use was 392. Although the RORs (95% CI) for acetaminophen were 0.25 (0.09–0.66), the RORs (95% CI) for the DPP-4 inhibitors were wholly significant and as follows; alogliptin, 8.02 (4.87–13.22); anagliptin, 10.84 (3.46–33.96); sitagliptin, 12.59 (9.86–16.06); trelagliptin, 13.77 (3.40–55.85); saxagliptin, 15.85 (5.87–42.79); linagliptin, 28.96 (21.38–39.23); omarigliptin, 43.79 (5.85–327.70); teneligliptin, 58.52 (42.75–80.10); and vildagliptin, 105.33 (88.54–125.30) (Table 1). Because most patients with diabetes receive combinations of medications, we excluded case subjects who received DPP-4 inhibitors. After such exclusion, significant RORs disappeared for case subjects receiving all the other antihyperglycemia drugs. Conversely, case subjects receiving DPP-4 inhibitors showed significant RORs even after exclusion of subjects who were receiving any other antihyperglycemia or candidate drugs, indicating that co-prescription bias was excluded. We stratified data by time trends of report and confirmed that the RORs of DPP-4 inhibitors were consistently significant over the period of 2012–2016. An analysis of ROR by therapeutic area with subjects who used antihyperglycemia drugs showed the RORs (95% CI) as follows: linagliptin, 2.67 (1.96–3.64); teneligliptin, 5.52 (4.01–7.60); vildagliptin, 12.09 (9.88–14.79); and DPP-4 inhibitors, 69.49 (34.50–139.99). Meanwhile, statistically significant associations disappeared for sitagliptin, saxagliptin, and alogliptin, implying a drug-specific effect. Vildagliptin, teneligliptin, and linagliptin, which show higher RORs than other DPP-4 inhibitors, possess lower substrate selectivity for DPP-4 or higher volume of distribution. It is possible that the inhibition of DPP-8 or DPP-9, but not that of DPP-4, in the skin evokes immunopathogenic reactions that result in the blister formation in BP. The number of males with BP taking DPP-4 inhibitors was significantly higher than the number of females with BP (male, 8,131 out of 222,567; female, 4,911 out of 215,460; $\chi^2 = 715.4$; $P < 2.2e\text{-}16$). There was no significant difference in the frequency of BP after adjustment for DPP-4 inhibitor use (with DPP-4 inhibitor use, 238 males out of 8,131,

Department of Endocrinology and Metabolism, Graduate School of Medicine, Yokohama City University, Yokohama, Japan

Corresponding author: Jun Shirakawa, jshira-tky@umin.ac.jp, or Yasuo Terauchi, terauchi-tky@umin.ac.jp.

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Table 1—Exposure to target drugs that had significant ROR values and numbers of BP case subjects

	With BP (*n*)	Without BP (*n*)	ROR	95% CI
All drugs	546	453,481		
All antihyperglycemia drugs	402	38,473	30.11	(24.89–36.44)
All antihyperglycemia drugs without DPP-4 inhibitors	10	25,672	0.31	(0.17–0.58)
DPP-4 inhibitors	392	12,811	87.56	(72.61–105.59)
Alogliptin	16	1,700	8.02	(4.87–13.22)
Anagliptin	3	231	10.84	(3.46–33.96)
Sitagliptin	76	5,752	12.59	(9.86–16.06)
Trelagliptin	2	121	13.77 (NA)	(3.40–55.85)
Saxagliptin	4	211	15.85	(5.87–42.79)
Linagliptin	47	1,470	28.96	(21.38–39.23)
Omarigliptin	1	19	43.79 (NA)	(5.85–327.70)
Teneligliptin	45	695	58.52	(42.75–80.10)
Vildagliptin	229	3,089	105.33	(88.54–125.30)
Without biguanides	305	9,790	57.36	(48.38–67.99)
Without glinides	359	11,988	70.70	(59.19–84.45)
Without sulfonylureas	295	8,517	61.40	(51.82–72.76)
Without thiazolidines	365	11,422	78.05	(65.25–93.36)
Without GLP-1 RAs	384	12,732	82.06	(68.23–98.68)
Without α-GIs	327	10,520	62.87	(52.92–74.69)
Without insulins	322	11,168	56.93	(47.96–67.59)
Without SGLT2is	379	11,529	87.00	(72.45–104.47)
Biguanides	88	6,589	13.03	(10.36–16.39)
Glinides	35	2,827	10.92	(7.74–15.41)
Sulfonylureas	100	13,814	7.14	(5.74–8.87)
Thiazolidines	28	4,866	4.98	(3.40–7.30)
GLP-1 RAs	8	848	7.94	(3.94–16.00)
α-GIs	70	9,306	7.02	(5.46–9.03)
Insulins	73	11,643	5.86	(4.57–7.50)
SGLT2is	13	2,183	5.04	(2.90–8.76)
Biguanides without DPP-4 inhibitors	1	3,568	NA	(0.03–1.65)
Glinides without DPP-4 inhibitors	2	2,004	NA	(0.21–3.32)
Sulfonylureas without DPP-4 inhibitors	3	9,520	0.26	(0.08–0.80)
Thiazolidines without DPP-4 inhibitors	1	3,477	NA	(0.03–1.69)
GLP-1 RAs without DPP-4 inhibitors	0	769	NA	—
α-GIs without DPP-4 inhibitors	5	7,015	0.59	(0.24–1.42)
Insulins without DPP-4 inhibitors	3	10,003	0.24	(0.08–0.76)
SGLT2is without DPP-4 inhibitors	0	901	NA	—
Other drugs				
Psoralens	1	27	NA	(4.18–227.18)
Ustekinumab	3	300	8.35	(2.67–26.11)
Galantamine hydrobromide	4	814	4.10	(1.53–11.00)
Hydrochlorothiazide	13	3,309	3.32	(1.91–5.76)
Nifedipine	36	10,680	2.93	(2.09–4.11)
Terbinafine	6	1,888	2.66	(1.19–5.95)
Amlodipine	88	31,732	2.55	(2.03–3.21)
Furosemide	67	24,344	2.47	(1.91–3.19)
Aspirin	73	28,778	2.28	(1.78–2.92)
Tiobutarit	7	2,769	2.11	(1.00–4.46)
Losartan	15	6,144	2.06	(1.23–3.44)
Psoralens without DPP-4 inhibitors	1	27	NA	(4.18–227.18)*
Ustekinumab without DPP-4 inhibitors	3	292	8.57	(2.74–26.82)*
Galantamine hydrobromide without DPP-4 inhibitors	0	760	NA	—
Hydrochlorothiazide without DPP-4 inhibitors	0	2,876	NA	—
Nifedipine without DPP-4 inhibitors	6	9,869	0.50	(0.22–1.12)
Terbinafine without DPP-4 inhibitors	4	1,848	1.80	(0.67–4.83)
Amlodipine without DPP-4 inhibitors	14	28,860	0.39	(0.23–0.66)
Furosemide without DPP-4 inhibitors	30	22,941	1.09	(0.75–1.58)
Aspirin without DPP-4 inhibitors	8	26,638	0.24	(0.12–0.48)
Tiobutarit without DPP-4 inhibitors	7	2,711	2.16	(1.02–4.56)*
Losartan without DPP-4 inhibitors	3	5,680	0.44	(0.14–1.36)
Negative control				
Acetaminophen	4	13,098	0.25	(0.09–0.66)
Without DPP-4 inhibitors	0	12,605	NA	—

A total of 42 drugs did not have significant ROR and were omitted here. NA, not applicable due to the low number of case subjects (<3). *Significant ROR even without DPP-4 inhibitors.

147 females out of 4,911, $\chi^2 = 0.05$, $P = 0.83$; without DPP-4 inhibitor use, 71 males out of 214,436, 76 females out of 210,549, $\chi^2 = 0.27$, $P = 0.60$). Thus, the higher number of males with DPP-4 inhibitor–related BP was presumably because DPP-4 inhibitors were used more often in males than in females. Most of the case subjects with BP were elderly people older than 60 years old. In 2015, NDB (National Database of Health Insurance Claims and Specific Health Checkups of Japan) Open Data Japan, a comprehensive prescription database, indicated that the distribution of DPP-4 inhibitor prescription in each 10-year age-group (from $<$40 to $\geq$90 years) was consistent with the adverse events induced by DPP-4 inhibitors in the JADER database. This suggests that advanced age is a risk factor for BP induced by DPP-4 inhibitor use, which is concordant with several previous reports, mainly from Europe, that showed BP was predominantly encountered in elderly people (2,3).

As the JADER database is a spontaneous reporting system, there are several limitations, such as underreporting, overreporting, missing data, mistakes in data entry, and a lack of control data. Especially among these, strong selection bias, so-called notoriety bias, must always be taken into consideration. In this study, we did not investigate the contribution of coexisting illnesses, drug dose, or the period of exposure. Further clinical monitoring and analytical observational studies that can evaluate the association are needed.

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