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Association between dipeptidyl peptidase-4 inhibitors and autoimmune disorders: Data mining of the spontaneous reporting system in Japan

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The main objective of this study is to conduct a disproportionality analysis of adverse events in the Japan Adverse Event Report (JADER) database and evaluate the risk of the DPP-4 inhibitor induced autoimmune disorder, the secondary objective is risk assessment of sex difference and age difference. The proportional reporting ratio (PRR) of frequency-based statistics and Bayesian estimates of the information components (IC) were calculated as a measure of signal detection. Sex difference and age difference were evaluated using signal score calculated from the PRR and the Chi-square. In patients taking DPP-4 inhibitors, 94 reports of autoimmune disorders were detected with both signals; PRR: 4.09, chi-square: 158.26 and IC: 1.66, 95 % confidence interval: 1.32–2.00). For other antidiabetic drugs, no signals were detected. The signal of males was PRR: 4.53, chi-square: 110.91 and signal score: 6.22, the signal of female was PRR: 3.53, chi-square: 47.65 and signal score: 5.12. About age difference, the signal scores were 6.71 for patients over 60 years and 0.56 for patients under 60 years old. This study suggests that the DPP-4 inhibitors, unlike other antidiabetic drugs, were associated with autoimmune disorders. Signals of the DPP-4 inhibitors induced autoimmune disorders were detected in both male and female, but no sex difference was observed, but age difference was observed. Especially attention should be paid to patients over 60 years old.

1. Introduction

Dipeptidyl peptidase-4 (DPP-4) inhibitors competitively inhibit DPP-4, which reduces blood glucose by increasing the secretion of incretin from gastrointestinal epithelial cells when food is ingested. Because incretin induced insulin secretion is dependent on glucose concentration, the DPP-4 inhibitors are less likely to cause hypoglycemia or weight gain compared to conventional insulin secretagogues such as sulfonylurea and glinide drugs. Thus, the DPP-4 inhibitors have become important for the treatment of type 2 diabetes, a disease that reduces insulin secretion.

However, DPP-4 is the same substance as cluster of differentiation 26 (CD26), a cell membrane surface antigen presents throughout the body that is also expressed in T cells (Reinhold et al. 2007; Alexandraki et al. 2006). For that reason, the DPP-4 inhibitors may affect the immune system. In fact, epidemiological reports have shown that the risk of developing infections is higher for patients taking the DPP-4 inhibitors than for those taking other antidiabetic drugs (Willemen et al. 2011).

The inhibition of CD26 activation by DPP-4 inhibitor administration appears to lead to immune suppression and not to immune activation followed by autoimmune disorders. However, a case autoimmune disorder, DPP-4 inhibitor induced bullous pemphigoid was reported (Mendonça et al. 2016).

Abbreviations: AE: adverse event, CI: confidence interval, CD29: cluster of differentiation 26, CXCR: C-X-C chemokine receptor 4, DPP: dipeptidyl peptidase, DPP-4-I: dipeptidyl peptidase-4 inhibitor, EBGM: empirical Bayes geometric mean, HLGT: high level group term, INF-g: interferon gamma, IL-2: interleukin-2, IC: information component, JADER: Japanese Adverse Drug Event Report database, PMDA: Pharmaceuticals and Medical Devices Agency, PT: preferred term, PRR: proportional reporting ratio, ROR: reporting odds ratio, SDF-1: stromal cell-derived factor-1, Th1: type 1 T helper cell.

Bullous pemphigoid occurs frequently among the elderly. The number of patients with bullous pemphigoid increases yearly as society ages, as does the number of cases of DPP-4 induced bullous pemphigoid (Hattori et al. 2013; Skandalis et al. 2012; Pasmatziet et al. 2011; Aouidad et al. 2013). Autoantibodies cause antigen-antibody reactions with basement membrane hemidesmosomal pemphigus antigens; bullous pemphigoid (BP) 180 and BP 230 in bullous pemphigoid, the most common form of autoimmune bullous pemphigoid (Hattori et al.. 2013). Death from bullous pemphigoid is not uncommon. A recent report found that the yearly death rate for bullous pemphigoid in the elderly is as high as 39.1 % (Nishie 2016).

Numerous studies have used disproportionality analyses for assessing the safety of drugs after marketing (Kose et al. 2017; Ohyama et al. 2017; Noguchi et al. 2018a, b). These "safety signals" include the proportional reporting ratio (PRR) (Evans et al. 2001) and the reporting odds ratio (ROR) (van Puijenbroek et al. 2002) similar to classical statistical methods, in addition to Bayesian estimates of the information component (IC) (Bate et al. 1998) and the empirical Bayes geometric mean (EBGM) (Szarfman et al. 2002), which are used to calculate parameters of prior distribution.

In addition to these detection methods, there is also a method using association rule mining (Noguchi et al. 2018c, d) and signal score (Noguchi et al. 2018a, b; Shirakuni et al. 2009).

Among the safety signals, the PRR and the ROR are easy to calculate; but when the number of reports is small, the signal values are unstable. In contrast, while it takes time to calculate the signal values using the IC and the EBGM, those signal values are relatively stable even when there are few reports (Fujita 2009).

In this study, we used the Japanese Adverse Drug Event Report database (JADER) published by the Pharmaceuticals and Medical Devices Agency (PMDA) to analyze signal detection in order to clarify the relationship between the DPP-4 inhibitors (and the antidiabetic drug) and autoimmune disorder.

Table 1: Suspected drugs targeted for the analysis

Class	Drug
Dipeptidyl peptidase-4 inhibitors (DPP-4-I)	Alogliptin
	Anagliptin
	Linagliptin
	Omarigliptin
	Saxagliptin
	Sitagliptin
	Teneligliptin
	Trelagliptin
	Vildagliptin
Sulfonylureas (SU)	Acetohexamide
	Glimepiride
	Glibenclamide
	Gliclazide
	Glyclopyramide
Glinides	Mitiglinide
	Nateglinide
	Repaglinide
Biguanides (BG)	Buformin
	Metformin
Thiazolidinediones (TZD)	Pioglitazone
α-Glucosidase inhibitors (α-GI)	Acarbose
	Miglitol
	Voglibose
Glucagon-like peptide-1 receptor agonists (GLP-1 RA)	Dulaglutide
	Exenatide
	Liraglutide
	Lixisenatide
Sodium glucose cotransporter-2 inhibitors	Ipragliflozin
	Empagliflozin
	Canagliflozin
	Dapagliflozin
	Tofogliflozin
	Luseogliflozin

2. Investigations and results

We analyzed gender, age, deficiency of the original disease, and age uncertainty such as "youth" and "elderly" using data from JADER (1st quarter of 2004 to the 4th quarter of 2015), excluding reports that did not include the primary disease. In this study, signals were calculated only for diabetic patients. Therefore, the total number of cases that could be used for analysis was 38,887. The suspected drugs targeted for the analysis were 8 classes of antidiabetic drugs, a total of 34 drugs (Table 1). Targeted adverse events (AEs) were tabulated with the preferred terms (PTs), including the high level group term (HLGT) "autoimmune disorder." Signal detection was carried out in accordance with the general detection criteria from previous reports in which the number of reports (n_{11}) exceeded 3, the PRR exceeded 2, and the chi-square exceeded 4 (Evans et al. 2001) and the lower limit of the IC 95 % confidence interval (CI) exceeded 0 (Szarfman et al. 2002). Sex difference and age difference were evaluated using signal score. Signal scores to be compared were calculated from the PRR and the chi-square of male and female or elderly and non-elderly patients, respectively, using the formula (1) proposed by Shirakuni et al. (2009). The detection criteria of the signal score is shown in Eq. (2) using 2 groups of patients belonging to group A and patients belonging to group B as an example (Noguchi et al. 2018a, b).

Analysis by pharmacological mechanisms of action revealed 94 reports of the DPP-4 inhibitor induced autoimmune diseases, with signals detected for PRR: 4.09, chi-square: 158.26 and the IC: 1.66, 95% CI: 1.32–2.00. In contrast, no signals were detected for other antidiabetic drugs (Table 2).

Table 2: Disproportionality analysis of 8 classes of antidiabetic drugs

Class	n_{11}	n_{1+}	PRR (chi-square)	IC (95%CI)
DPP-4-I	94	3,276	4.09* (158.26)	1.66* (1.32 – 2.00)
SU	15	1,443	1.18 (0.25)	0.21 (-0.53 – 0.95)
Glinide	2	514	0.44 (0.94)	-0.89 (-2.57 – 0.79)
BG	6	889	0.76 (0.24)	-0.35 (-1.45 – 0.76)
TZD	3	1,381	0.24 (6.51)	-1.73 (-3.18 – -0.28)
α-GI	7	1,190	0.66 (0.91)	-0.53 (-1.57 – 0.50)
GLP-1-RA	3	429	0.79 (0.02)	-0.27 (-1.72 – 1.19)
SGLT-2-I	12	1,259	1.08 (0.01)	0.09 (-0.72 – 0.91)

n_{11}: the number of interest drug induced autoimmune disease, n_{1+}: the number of interest drug induced all adverse events, PRR: the proportional reporting ratio, IC: the information components, CI: confidence interval, DPP-4-I: dipeptidyl peptidase-4 inhibitor, SU: sulfonylurea, BG: biguanide, TZD: Thiazolidinedione, α-GI: a-glucosidase inhibitor, GLP-1-RA: glucagon like peptide-1 receptor agonist, SGLT-2-I: sodium-dependent glucose transporter 2 inhibitor.

Analysis of the DPP-4 inhibitors revealed PRR and IC signals for the following drugs: alogliptin (n_{11}: 8, PRR: 2.66, chi-square: 6.60 and IC: 1.15, 95% CI: 0.16–2.13), linagliptin (n_{11}: 13, PRR: 4.56, chi-square: 31.69 and IC: 1.82, 95% CI: 1.02–2.63), sitagliptin (n_{11}: 41, PRR: 4.32, chi-square: 89.95 and IC: 1.87, 95% CI: 1.39–2.35), and vildagliptin (n_{11}: 30, PRR: 3.03, chi-square: 35.65 and IC: 1.42; 95% CI: 0.88–1.97) (Table 3).

Table 3: Disproportionality analysis of dipeptidyl peptidase-4 inhibitors

Drug	n_{11}	n_{1+}	PRR (chi-square)	IC (95%CI)
DPP-4-I	94	3,276	4.09* (158.26)	1.66* (1.32 – 2.00)
Alogliptin	8	345	2.66* (6.60)	1.15* (0.16 – 2.13)
Anagliptin	1	72	1.57 (0.03)	0.28 (-1.79 – 2.35)
Linagliptin	13	332	4.56* (31.69)	1.82* (1.02 – 2.63)
Omarigliptin	0	2	NA	NA
Saxagliptin	1	70	1.62 (0.02)	0.30 (-1.78 – 2.37)
Sitagliptin	41	1,181	4.32* (89.95)	1.87* (1.39 – 2.35)
Teneligliptin	3	98	3.48 (3.11)	1.09 (-0.39 – 2.57)
Trelagliptin	1	19	5.96 (0.66)	0.76 (-1.38 – 2.91)
Vildagliptin	30	1,189	3.03* (35.65)	1.42* (0.88 – 1.97)

n_{11}: the number of interest dipeptidyl peptidase-4 inhibitor induced autoimmune disease, n_{1+}: the number of interest dipeptidyl peptidase-4 inhibitor induced all adverse events, PRR: the proportional reporting ratio, IC: the information components, CI: confidence interval, DPP-4-I: dipeptidyl peptidase-4 inhibitor.

The sex difference of PRR signals and the signal score are shown in Table 4. The signal of males was n_{11}:58, PRR: 4.53, chi-square: 110.91, the signal of female was n_{11}:36, PRR: 3.53, chi-square: 47.65. The signals were detected in both sexes. However, the signal scores were 6.22 for males and 5.12 for females. From this result, a sex difference was not observed.

Table 4: Signals of each sex group

sex	n_{11}	n_{1+}	PRR (chi-square)	signal score
Total	94	3,276	4.09* (158.26)	
Male	58	1,995	4.53* (110.91)	6.22
Female	36	1,281	3.53* (47.65)	5.12

n_{11}: the number of dipeptidyl peptidase-4 inhibitor induced autoimmune disease, n_{1+}: the number of dipeptidyl peptidase-4 inhibitor induced all adverse events, PRR: the proportional reporting ratio, IC: the information components.

Signals for each age group and the signal score of patients over 60 years and under 60 years are shown in Table 5. The PRR signals for each age group were detected only in patients over 60 years, the IC signals for each age group were detected only in patients over 60 years (excluding patients over 90 years).

Table 5: Signals of each age group

Age	n_{11}	n_{1+}	PRR (chi-square)	IC (95%CI)
Total	94	3,276	4.09* (158.26)	1.66* (1.32 – 2.00)
< 40	0	36	NA	NA
40 – 49	2	136	1.51 (0.01)	0.30 (-1.50 – 2.09)
50 – 59	5	333	2.11 (1.63)	0.73 (-0.54 – 2.00)
60 – 69	21	861	2.92* (19.96)	1.24* (0.56 – 1.92)
70 – 79	39	1,141	5.08* (84.02)	1.80* (1.27 – 2.33)
80 – 89	22	672	10.69* (74.39)	2.04* (1.27 – 2.81)
90 ≤	5	97	22.99* (13.50)	1.41 (-0.21 – 3.04)
< 60	7	505	1.64 (1.03) signal value: 0.52	0.54 (-0.54 – 1.62)
60 ≤	87	2,771	4.74* (173.29) signal value: 6.71	1.78* (1.42 – 2.14)

n_{11}: the number of dipeptidyl peptidase-4 inhibitor induced autoimmune disease, n_{1+}: the number of dipeptidyl peptidase-4 inhibitor induced all adverse events, PRR: the proportional reporting ratio, IC: the information components, CI: confidence interval.

The signal for patients over 60 was n_{11}: 87, PRR: 4.74, chi-square: 173.29 and IC: 1.78, 95 % CI: 1.42–2.14, the signal of patients under 60 was n_{11}: 7, PRR: 1.64, chi-square: 1.03 and IC: 0.54, 95 % CI: -0.54–1.62. The signal scores were 6.71 for patients over 60 years and 0.52 for patients under 60 years.

The signals of diseases classified as autoimmune disorders are shown in Table 6. Diseases in which both PRR and IC signals were detected were pemphigoid (n_{11}: 45, PRR: 34.94, chi-square: 343.82 and IC: 2.93, 95 % CI: 2.36–3.49), rheumatoid arthritis (n_{11}: 16, PRR: 15.81, chi-square: 84.03 and IC: 2.34, 95 % CI: 1.45–3.23), autoimmune pancreatitis (n_{11}: 7, PRR: 76.09, chi-square: 55.01 and IC: 2.19, 95 % CI: 0.78–3.59), polymyalgia rheumatica (n_{11}: 5, PRR: 7.76, chi-square: 13.15 and IC: 1.52, 95 % CI: 0.09–2.94).

Table 6: Signals of DPP-4-Is induced diseases classified as autoimmune disease

DPP-4-I induced ADR	n_{11}	(%)	PRR (chi-square)	IC (95%CI)
Autoimmune disorders (HLGT)	94	100	4.09* (158.26)	1.66* (1.32 – 2.00)
Pemphigoid	45	47.9	34.94* (343.82)	2.93* (2.36 – 3.49)
Rheumatoid arthritis	16	17.0	15.81* (84.03)	2.34* (1.45 – 3.23)
Immunethrombocytopenic purpura	7	7.4	2.54* (4.01)	0.93 (-0.19 – 2.05)
Autoimmune pancreatitis	7	7.4	76.09* (55.01)	2.19* (0.78 – 3.59)
Polymyalgia rheumatica	5	5.3	7.76* (13.15)	1.52* (0.09 – 2.94)
Insulin autoimmune syndrome	3	3.2	4.66* (3.56)	1.05 (-0.63 – 2.74)
Basedow's disease	3	3.2	8.15* (6.76)	1.26 (-0.51 – 3.02)
Collagen disorder	2	2.1	21.74 (6.72)	1.17 (-1.04 – 3.37)
Glomerulonephritis rapidly progressive	1	1.1	0.68 (0.004)	-0.33 (-2.48 – 1.82)
Cholangitis sclerosing	1	1.1	3.62 (0.09)	0.49 (-1.92 – 2.91)
Evans syndrome	1	1.1	10.87 (0.71)	0.67 (-1.96 – 3.31)
Autoimmune hepatitis	1	1.1	1.36 (0.10)	0.12 (-2.12 – 2.35)
Autoimmune haemolytic anaemia	1	1.1	1.36 (0.10)	0.12 (-2.12 – 2.35)
Interstitial granulomatous dermatitis	1	1.1	NA	NA
Sjogren's syndrome	1	1.1	5.44 (0.26)	0.58 (-1.92 – 3.08)

DPP-4-I: dipeptidyl peptidase-4 inhibitor, ADR: adverse drug event, n_{11}: the number of DPP-4-Is induced diseases classified as autoimmune disease, PRR: the proportional reporting ratio, IC: the information components, CI: confidence interval.

3. Discussion

In this study, we focused on the possibility that DPP-4 inhibitors affect immunomodulatory function. Disproportionality analysis of data from JADER was used to compare the association between immunomodulatory function of the DPP-4 inhibitors to that of other antidiabetic drugs. Furthermore, sex differences and age differences were investigated for the association of onset of autoimmune disorders in patients receiving DPP4 inhibitors.

Statistical studies have shown that using disproportionality analysis to calculate the PRR or the ROR is easy, but the signals are unstable when there are only few reports (Fujita 2009).

Since the signal of each DPP-4 inhibitor was also calculated, the number of reports that can be used for signal calculation is small. Therefore, we used not only PRR but also IC that can detect a stable signal even when the number of reports is small, so we could evaluate the association between the DPP-4 inhibitors and autoimmune diseases. Nevertheless, many confounding factors can affect autoimmunity and the analysis of our results. For instance, among antidiabetic drugs, the signal for "autoimmune diseases" was detected only in DPP-4 inhibitors; but while both the PRR and the IC signals were detected in four of the DPP-4 inhibitors.

No signals were detected for trelagliptin, which may have behaved differently from other formulations of the DPP-4 inhibitors because it is a weekly formulation. Two AEs were reported for omarigliptin, another weekly formulation released in Japan in September 2015, but neither of them was related to autoimmune diseases. Thus, further analysis of weekly formulations is necessary once enough case reports have accumulated.

While no sex differences were seen, influence of age was obvious. In the survey of each age group, both the PRR and the IC signals were detected in the age group from 60 to 89 years. So the signal score of over 60 years old patients was 10 times higher than that of patients under 60 years old. Based on this study, patients who are at least over 60 years old and receiving DPP4 inhibitor treatment should be monitored for autoimmune diseases.

Autoimmune disorders caused by the DPP-4 inhibitors include pemphigoid, rheumatoid arthritis, immunologic thrombocytopenic purpura, autoimmune pancreatitis, and Polymyalgia rheumatica.

Another consideration is that DPP-4 is the same substance as the cell surface antigen CD26 present throughout the body. Among the CD26-positive T cells cytokine-secreting cells exist, such as type 1 T helper (Th1) lymphocytes that produce interleukin-2 (IL-2) and interferon gamma (INF-g) and are believed to be involved in immune function regulation (e.g., induction of B cell immunoglobulin production) (Hattori et al. 2013).

In addition, blood DPP-4 concentrations are reportedly lower in patients and mice with rheumatoid arthritis than in those without rheumatoid arthritis. Low blood DPP-4 concentrations in laboratory animals can raise the activity of C-X-C chemokine receptor 4 (CXCR4) and its ligand stromal cell-derived factor-1 (SDF-1) (Busso et al. 2005).

Epidemiological studies (Willemen et al. 2011) have shown that DPP-4 inhibitors increase the risk of infection compared to other antidiabetic drugs, and there are case reports of possible DPP-4 inhibitor drug-induced fever (Anno et al. 2013, Matsubara et al. 2017).

On the other hand, there are not only reports of DPP-4 inhibitors induced autoimmune disorders from the the spontaneous reporting system, but also several case reports, for example, DPP-4 inhibitor induced bullous pemphigoid (Mendonça et al. 2016; Yoshiji et al. 2018) and rheumatoid arthritis (Yokota and Igaki 2012).

Furthermore, we must also consider that in addition to inhibiting DPP-4, the DPP-4 inhibitors have a mild inhibitory effect against other DPP-4 related enzymes such as DPP-8 and DPP-9 (Kirby et al. 2013). Unlike DPP-4, DPP-8 and DPP-9 are present in the cytoplasm of cells such as lymphocytes. DPP-8/9-selective inhibitors reportedly potentiate T cell activity *in vitro* (Lankas et al. 2005). Vildagliptin has lower DPP-4 selectivity and a relatively stronger DPP-8/9 inhibitory effect than sitagliptin (Lee et al. 2008). In this study, the magnitude of the DPP-4 inhibitor signals for autoimmune disease did not correlate with the strength of DPP-8/9 inhibitory effects. However, the magnitude of the signal does not necessarily correlate with the strength of pharmacological action (Noguchi et al. 2018b). There are reports that large doses of vildagliptin (high enough to inhibit DPP-8/9) are not toxic to mice (Burkey et al. 2008). Therefore, further studies are needed to investigate the influence of DPP-4 inhibitors on DPP-8/9.

Finally, because the medical database used in this study is based on spontaneous reporting, only some of the AEs experienced in clinical settings had been registered. Careful interpretation of detected signals is necessary to mitigate reporting biases such as the notoriety effect (the number of reported AEs increases when the public associates a drug with an AE) and the ripple effect (the number of reported AEs for one drug increases because of the notoriety of another drug in the same class) (Pariente et al. 2007).

This study suggests that DPP-4 inhibitors induce autoimmune disorders. However, the number of reports currently registered in JADER is limited and needs more detailed analysis. The authors recommend further clinical research using real world data, and a detailed meta-analysis with more stringent clinical and scientific analyses be conducted.

4. Experimental

4.1. Data source

Authors do not own the data because the Japanese authority, PMDA, does not does not permit sharing the Japanese Adverse Drug Event Report database (JADER) directly. Data owned by PMDA can be accessed directly here:
http://www.info.pmda.go.jp/fukusayoudb/CsvDownload.jsp (only in Japanese).

4.2. Identification of the suspected drugs and definition of autoimmune disease

The AEs registered in JADER were the PTs used in the Medical Dictionary for Regulatory Activities/ Japanese version (MedDRA/J). In this study, the targeted AEs were tabulated with all PTs including the HLGT "autoimmune disorder". Analysis was carried out by linking with all PTs registered in HLGT. (In diabetic patients, 15 PT shown in Table 6 were registered in HLGT.)

In this study, the patients with autoimmune disorder as the primary disease were not excluded in advance. In JADER, the cases registered are the AEs caused by the suspected drugs. Therefore, we considered that the deterioration of the patient's primary disease is also an AE in this study.

4.3. Disproportionality analysis

The number of reported AEs due to the use of the targeted drug was not based on the number of drug-AEs pair. Rather, the number of reports of adverse events due to the use of the target drugs was counted based on the number of cases.

Signal detection was carried out in accordance with the general detection criteria from previous reports in which the number of reports (n_{11}) exceeded 3, the PRR exceeded 2, and the chi-square exceeded 4 (Evans et al. 2001) and the lower limit of the IC 95 % CI exceeded 0 (Szarfman et al. 2002).

4.4. Comparison of the signal scores

Sex and age differences were evaluated using the signal score. The signal scores to be compared were calculated from the PRR and the chi-square of male and female, or elderly and non-elderly patients, respectively, using formula (1) proposed by Shirakuni et al. (2009):

$$\text{The signal score} = \ln(\text{PRR}) + \ln(\text{chi-square}) \quad \ldots(1)$$

The detection criteria of the signal score is shown in Eq. (2) using two groups of patients belonging to group A and patients belonging to group B as an example (Noguchi et al. 2018a, b):

$$\text{The signal score of group A} > 2\times(\text{the signal score of group B}) \quad \ldots(2)$$

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References

Alexandraki K, Piperi C, Kalofoutis C, Singh J, Alaveras A, Kalofoutis A (2006) Inflammatory process in type 2 diabetes: The role of cytokines. Ann N Y Acad Sci 1084: 89-117.

Anno T, Hashiramoto M, Tanabe A, Nakashima K, Okauchi S, Kamei S, Matsuki M, Mune T, Kaku K (2013) A case of type 2 diabetes mellitus associated with a drug-induced fever caused by a DPP-4 inhibitor, sitagliptin. J Japan Diab Soc 56: 292-297.

Aouidad I, Fite C, Marinho E, Deschamps L, Crickx B, Descamps V (2013) A case report of bullous pemphigoid induced by dipeptidyl peptidase-4 inhibitors. JAMA Dermatol 149: 243-245.

Bate A, Lindquist M, Edwards IR, Olsson S, Orre R, Lansner A, De Freitas RM (1998) A Bayesian neural network method for adverse drug reaction signal generation. Eur J Clin Pharmacol 54: 315–321.

Burkey BF, Hoffmann PK, Hassiepen U, Trappe J, Juedes M, Foley JE (2008) Adverse effects of dipeptidyl peptidases 8 and 9 inhibition in rodents revisited. Diabetes Obes Metab 10: 1057-1061.

Busso N, Wagtmann N, Herling C, Chobaz-Peclat V, Bischof-Delaloye A, So A, Grouzmann E (2005) Circulating CD26 is negatively associated with inflammation in human and experimental arthritis. Am J Pathol 166: 433-442.

Evans SJ, Waller PC, Davis S (2001) Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidemiol Drug Saf 10: 483–486.

Fujita T (2009) Signal detection of adverse drug reactions. Jpn J Pharmacoepidemiol 14: 27-36.

Hattori A, Imai M, Moriai T (2013) A case of bullous pemphigoid associated with sitagliptin treatment. J Jpn Diabetes Soc 56: 881-885.

Kirby M, Yu DM, O'Connor S, Gorrell MD (2010) Inhibitor selectivity in the clinical application of dipeptidyl peptidase-4 inhibition. Clin Sci 118: 31-41.

Kose E, Uno K, Hayashi H (2017) Evaluation of the expression profile of extrapyramidal symptoms due to antipsychotics by data mining of Japanese Adverse Drug Event Report (JADER) Database. Yakugaku Zasshi 137: 111-120.

Lankas GR, Leiting B, Roy RS, Eiermann GJ, Beconi MG, Biftu T, Chan CC, Edmondson S, Feeney WP, He H, Ippolito DE, Kim D, Lyons KA, Ok HO, Patel RA, Petrov AN, Pryor KA, Qian X, Reigle L, Woods A, Wu JK, Zaller D, Zhang X, Zhu L, Weber AE, Thornberry NA (2005) Dipeptidyl peptidase IV inhibition for the treatment of type 2 diabetes: potential importance of selectivity over dipeptidyl peptidases 8 and 9. Diabetes 54: 2988-2994.

Lee B, Shi L, Kassel DB, Asakawa T, Takeuchi K, Christopher RJ (2008) Pharmacokinetic, pharmacodynamic, and efficacy profiles of alogliptin, a novel inhibitor of dipeptidyl peptidase-4, in rats, dogs, and monkeys. Eur J Pharmacol 589: 306-314.

Matsubara F, Nagai Y, Yamada Y, Ishii S, Kato H, Tanaka Y (2017) A case of alogliptin-induced drug fever. J Japan Diab Soc 60: 548-553.

Mendonça FM, Martín-Gutierrez FJ, Ríos-Martín JJ, Camacho-Martinez F (2016) Three cases of bullous pemphigoid associated with dipeptidyl peptidase-4 inhibitors - one due to linagliptin. Dermatology 232: 249-253.

Nishie W (2016) DPP-4 Inhibitor-associated bullous pemphigoid. Nishi Nihon Hifuka 78: 583-588.

Noguchi Y, Ueno A, Katsuno H, Otsubo M, Yoshida A, Kanematsu Y, Sugita I, Tachi T, Tsuchiya T, Teramachi H (2018a) Analyses of non-benzodiazepine-induced adverse events and prognosis in elderly patients based on the Japanese adverse drug event report database. J Pharm Health Care Sci 4:10.

Noguchi Y, Katsuno H, Ueno A, Otsubo M, Yoshida A, Kanematsu Y, Sugita I, Esaki H, Tachi T, Tsuchiya T, Teramachi H (2018b) Signals of gastroesophageal reflux disease caused by incretin-based drugs: a disproportionality analysis using the Japanese adverse drug event report database. J Pharm Health Care Sci 4: 15.

Noguchi Y, Ueno A, Otsubo M, Katsuno H, Sugita I, Kanematsu Y, Yoshida A, Esaki H, Tachi T, Teramachi H (2018c) A new search method using association rule mining for drug-drug interaction based on spontaneous report system. Front Pharmacol 9: 197.

Noguchi Y, Ueno A, Otsubo M, Katsuno H, Sugita I, Kanematsu Y, Yoshida A, Esaki H, Tachi T, Teramachi H (2018d) A simple method for exploring adverse drug events in patients with different primary diseases using spontaneous reporting system, BMC Bioinformatics 19: 124.

Ohyama K, Kawakami H, Inoue M (2017) Blood pressure elevation associated with topical prostaglandin F2α analogs: an analysis of the different spontaneous adverse event report databases. Biol Pharm Bull 40: 616–620.

Pariente A, Gregoire F, Fourrier-Reglat A, Haramburu F, Moore N (2007) Impact of safety alerts on measures of disproportionality in spontaneous reporting databases: the notoriety bias. Drug Saf 30: 891-898.

Pasmatzi E, Monastirli A, Habeos J, Georgiou S, Tsambaos D (2011) Dipeptidyl peptidase-4 inhibitors cause bullous pemphigoid in diabetic patients: report of two cases. Diabetes Care 34: e133.

Reinhold D, Biton A, Goihl A, Pieper S, Lendeckel U, Faust J, Neubert K, Bank U, Tager M, Ansorge S, Brocke S (2007) Dual inhibition of dipeptidyl peptidase IV and aminopeptidase N suppresses inflammatory immune responses. Ann N Y Acad Sci 1110: 402-409.

Shirakuni Y, Okamoto K, Kawashita N, Yasunaga T, Takagi T (2009) Signal detection of drug complications applying association rule learning for Stevens-Johnson Syndrome. J Com Aid Chem 10: 118-127.

Skandalis K, Spirova M, Gaitanis G, Tsartsarakis A, Bassukas ID (2012) Drug-induced bullous pemphigoid in diabetes mellitus patients receiving dipeptidyl peptidase-IV inhibitors plus metformin. J Eur Acad Dermatol Venereol 26: 249-253.

Szarfman A, Machado SG, O'Neill RT (2002) Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. Drug Saf 25: 381–392.

van Puijenbroek EP, Bate A, Leufkens HG, Lindquist M, Orre R, Egberts AC (2002) A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. Pharmacoepidemiol Drug Saf 11: 3–10.

Willemen MJ, Mantel-Teeuwisse AK, Straus SM, Meyboom RH, Egberts TC, Leufkens HG (2011) Use of dipeptidyl peptidase-4 inhibitors and the reporting of infections: a disproportionality analysis in the World Health Organization VigiBase. Diabetes Care 34: 369-374.

Yokota K, Igaki N (2012) Sitagliptin (DPP-4 inhibitor)-induced rheumatoid arthritis in type 2 diabetes mellitus: a case report. Intern Med 51: 2041-2044.

Yoshiji S, Murakami T, Harashima SI, Ko R, Kashima R, Yabe D, Ogura M, Doi K, Inagaki N (2018) Bullous pemphigoid associated with dipeptidyl peptidase-4 inhibitors: A report of five cases. J Diabetes Invest 9: 445-447.