

# Use of Dipeptidyl Peptidase-4 Inhibitors and the Reporting of Infections: A Disproportionality Analysis in the World Health Organization Vigibase

MARJOLEIN J. WILLEMEN, PHARM<sup>1,2</sup>  
 AUKJE K. MANTEL-TEEUWISSE, PHD<sup>1,2</sup>  
 SABINE M. STRAUS, PHD<sup>2,3</sup>

RON H. MEYBOOM, PHD<sup>1,4</sup>  
 TOINE C. EGBERTS, PHD<sup>1,5</sup>  
 HUBERT G. LEUFKENS, PHD<sup>1,2</sup>

**OBJECTIVE**—Dipeptidyl peptidase-4 (DPP-4) inhibitors are a new class of antidiabetic drugs. They inactivate incretin hormones but also have many other effects throughout the body, among which are effects on the immune system. This might result in an increased infection risk. This study assessed the association between use of DPP-4 inhibitors and the reporting of infections.

**RESEARCH DESIGN AND METHODS**—A nested case-control was conducted using Vigibase, the World Health Organization-Adverse Drug Reactions (WHO-ADR) database. The base cohort consisted of ADRs for antidiabetic drugs (Anatomical Therapeutic Chemical code A10). Cases were defined as ADRs of infection according to the Medical Dictionary for Regulatory Activities (MedDRA) classification system. All other ADRs were considered controls. Reporting odds ratios (RORs) were calculated to estimate the strength of the association between different classes of antidiabetic drugs and the reporting of infections.

**RESULTS**—We identified 305,415 suspected ADRs involving antidiabetic drugs in 106,469 case reports, of which 8,083 involved DPP-4 inhibitors monotherapy. Overall, the reporting of infections was higher for patients using DPP-4 inhibitors compared with users of biguanides (ROR 2.3 [95% CI 1.9–2.7]). Reporting of upper respiratory tract infections (ROR 12.3 [95% CI 8.6–17.5]) was significantly associated with use of DPP-4 inhibitors.

**CONCLUSIONS**—This study indicates an increased reporting of infections, in particular upper respiratory tract infections, for users of DPP-4 inhibitors compared with users of other antidiabetic drugs. However, the limitations of spontaneous reporting systems (e.g., underreporting, the Weber-effect, reporting bias) should be taken into account. Therefore, further research is needed to evaluate this suspicion and the underlying mechanism.

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**D**ipeptidyl peptidase-4 (DPP-4) inhibitors are a new class of antidiabetic drugs, with three products currently available on the market: sitagliptin, vildagliptin, and saxagliptin (1–3). The inactivation of incretin hormones (glucagon-like

peptide-1 and glucose-dependent insulinotropic polypeptide) by DPP-4 inhibitors results in a rise in insulin from pancreatic  $\beta$ -cells and a decrease in glucagon from pancreatic  $\alpha$ -cells. As a consequence, DPP-4 inhibitors improve glycemic control

by reducing fasting and postprandial glucose concentrations in patients with type 2 diabetes (1).

DPP-4 is assumed to have many other functions in the human physiology due to its presence on the surface of many different cell types, but these effects are still largely unknown. The role of DPP-4 in immune regulation is better defined and includes induction of transforming growth factor- $\beta$ 1 in activated T cells and suppression of production of inflammatory cytokines by T cells (4), effects on cell growth, differentiation, and apoptosis (5,6). The immunomodulating effect has given rise to concerns regarding a possible increase in the occurrence of infections (1–3).

Nasopharyngitis, upper respiratory tract (URTI), and related infections (acute bronchitis, pharyngitis, sinusitis, and rhinitis) were the most commonly reported infections for the active substances compared with the reference intervention in clinical trial programs (1–3). However, pooled analyses for vildagliptin and saxagliptin did not indicate an increased risk of infections compared with the reference group (7,8). In the three European Union (EU) Risk Management Plans (a mandatory part of marketing applications since November 2005 [9]) for the approved DPP-4 inhibitors, “infections” were defined as important identified risks that require further evaluation. Postauthorization safety studies specifically evaluating the risk of hospitalization due to infections are currently being conducted for vildagliptin and saxagliptin (2,3). For sitagliptin, the risk for infections will be further evaluated through an in-depth analysis of the safety results of the ongoing and planned clinical trials (1).

Data on a possible direct relation between diabetes mellitus and infections are inconclusive. Several studies investigated a possible association between diabetes mellitus and alterations of the immune system (10,11). Some epidemiologic studies showed that these patients are at an increased risk for common

From the <sup>1</sup>Division of Pharmacoepidemiology and Clinical Pharmacology, Faculty of Science, Utrecht Institute for Pharmaceutical Sciences, Utrecht, the Netherlands; the <sup>2</sup>Medicines Evaluation Board, The Hague, the Netherlands; the <sup>3</sup>Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, the Netherlands; the <sup>4</sup>World Health Organization Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre, Uppsala, Sweden; and the <sup>5</sup>Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht, the Netherlands.

Corresponding author: Aukje K. Mantel-Teeuwisse, a.k.mantel@uu.nl.

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infections (12–15), but evidence from clinical trials is limited and inconsistent (16). Disease progression may have an effect on the occurrence of infections; thus, more severely ill patients might be at an increased risk of infections (17). To our knowledge, no studies have specifically investigated the relation between the use of DPP-4 inhibitors and infections as adverse drug reactions (ADRs). Therefore, the aim of the current study was to assess the relation between different classes of antidiabetic drugs and the reporting of infections.

## RESEARCH DESIGN AND METHODS

### Setting and study design

Data were obtained from the International Drug Monitoring Program of the World Health Organization (WHO). The WHO global individual case safety report (ICSR) database, Vigibase, is maintained by the Uppsala Monitoring Centre and contains summaries of suspected spontaneous case reports originally summated by health care professionals and patients to national pharmacovigilance centers in 98 countries worldwide. As of May 2010, this database contained >5 million case reports of suspected ADRs regarding specific, but anonymous, patients. The reports contain administrative data, patient data, ADR data, medication data, and additional information. The information in these reports is not homogenous, at least with regard to origin, completeness of documentation, or the likelihood that the suspected drug caused the adverse events (18). ADRs are coded according to the Adverse Reaction Terminology (WHO-ART) and Medical Dictionary for Regulatory Activities (MedDRA; www.who-umc.org).

This study was designed as a nested case-control study. The base cohort consisted of all ADRs associated with the use of any antidiabetic drug (Anatomical Therapeutic Chemical [ATC] code A10), including oral antidiabetic drugs and insulins, in the period 1999 through 2009.

### Definition of cases and controls

Cases were defined as ADRs classified as an infection. Infections were defined by means of MedDRA adverse reaction terms, including all relevant high-level group terms and lower-level terms. All infections from the System Organ Class (SOC) “Infections and Infestations” and infections reported in other SOCs identified

through a manual search were defined as cases. All reports containing other ADRs were considered as controls. We grouped the infections on the first sublevel (high-level group terms) of MedDRA and looked at URTI (e.g., sinusitis and nasopharyngitis), lower respiratory tract infections (LRTI, e.g., bronchitis and pneumonia), and urinary tract infections (UTI; e.g., cystitis and pyelonephritis). Because of low numbers, all other infections were combined.

### Exposure definition

Exposure to antidiabetic drugs was the determinant that was investigated. Antidiabetic drugs were subclassified based on the Anatomical Therapeutic Chemical (ATC) classification system of the WHO (www.whocc.no): biguanides (ATC code A10BA), sulfonylurea derivatives (A10BB), thiazolidinediones (A10BG), DPP-4 inhibitors (A10BH), insulins, and analogs (A10A). When multiple antidiabetic drugs were reported for a certain ADR, this was classified as combination therapy, irrespective of whether a drug reported was classified as “suspected” or as a comedication.

### Potential confounding factors

Potential confounding factors retrieved from the case reports included age and gender of the patient, reporting year, reporting region (Europe, North America, rest of the world), and reporter type, including physician, pharmacist, other caregiver, pharmaceutical company (indirectly obtained from a health care professional), and patient/consumer. Concomitant use of medication affecting the immune system, defined as reporting one of these drugs as a concomitant drug for an ADR, was taken into account when recorded, including antibiotics (ATC code J01), corticosteroids for systemic use (H02), and immunosuppressants (L04).

### Data analysis

Descriptive statistics were used to summarize the baseline characteristics of the case reports. Unconditional logistic regression analysis was used to estimate the strength of the association between use of antidiabetic drugs and reporting of infections and expressed as reporting odds ratios (RORs) with corresponding 95% CIs. Biguanides were the reference group. Owing to low numbers, combination therapy was analyzed on an aggregated level, not on an individual drug-drug combination level. We focused on infections in general and more specifically on

the high-level group terms URTI, LRTI, and UTI. Adjusted analyses were conducted with all potential confounders included in the model.

More ADRs were usually reported for one case report, and therefore it was possible that one case report contained more than one ADR of an infection. To test the effect of multiple ADRs reported in one case report, we analyzed the data on the level of case reports (one case report generally represented one patient).

In the U.S., DPP-4 inhibitors are indicated for monotherapy for the treatment of diabetes mellitus, whereas in the EU, these medicines are only indicated for combination therapies. To check whether this affected the results of this study, we performed a sensitivity analysis by analyzing the data for the U.S. and the rest of the world separately. In addition, to study the effect of the type of reporter (health care professional or consumer) on the outcome, we performed a sensitivity analysis in which the reports were assessed according to the type of reporter. Statistical analysis was done using SPSS 16.0 statistical software (SPSS Inc., Chicago, IL).

**RESULTS**—From the WHO Vigibase we identified 305,415 suspected ADRs related to the use of antidiabetic drugs in 106,469 case reports in the study period 1999 through 2009. Patients were a mean age of 59.7 years (SD, 14.3) and 59.6% were women. A total of 288,434 reports (94.4%) reports involved one antidiabetic drug, 14,057 (4.6%) reported a combination of two antidiabetic drugs, and 2,924 (1.0%) reported three or more antidiabetic drugs (Table 1). Overall, the most commonly reported infections on the level of MedDRA lower-level terms were pneumonia (11.8%), nasopharyngitis (10.1%), UTIs (6.2%), infection not otherwise specified (5.5%), sinusitis (5.1%), and bronchitis (4.8%). All other types of infection were reported in <4.5% of the reports related to infections.

A total of 242 infections were reported as a MedDRA term in 212 case reports for DPP-4 inhibitors, of which 188 (88.7%) reported one infection. Of the 24 case reports (11.3%) with multiple infections, 12 (50%) reported a nonspecific infection term, such as “infection” or “URTI,” combined with a more specific infection term, such as “nasopharyngitis” or “cystitis” (see the Supplementary Data for a summary of the infections according to the MedDRA lower-level term).

**Table 1—Baseline characteristics of all spontaneous reports for antidiabetic drugs in the WHO VigiBase (1999–2009)**

Variable	Spontaneous reports (N = 305,415)
Patient age, mean (SD), years	59.7 (14.3)
Age (missing)	63,212 (20.7)
Female sex	182,130 (59.6)
Sex (missing)	9,100 (3.0)
Reporter	
Health care professional	92,896 (30.4)
Nonhealth care professional	129,287 (42.3)
Study/literature	218 (0.1)
Unknown	45,308 (14.8)
Other	37,706 (12.3)
Reporting year	
1999–2004	93,255 (30.5)
2005–2009	212,160 (69.5)
Region	
Europe	19,252 (6.3)
United States	273,079 (89.4)
Other	13,084 (4.3)
Antidiabetic drugs involved	
Monotherapy	288,434 (94.4)
Biguanides	21,763 (7.1)
Sulfonylurea derivative	16,675 (5.5)
Thiazolidinediones	57,814 (18.9)
Dipeptidyl peptidase-4 inhibitors	8,083 (2.6)
Insulin	80,347 (26.3)
Dual therapy	14,057 (4.6)
2 oral antidiabetics	11,991 (3.9)
Biguanide, sulfonylurea derivative	2,413 (0.8)
Biguanide, thiazolidinediones	1,087 (0.4)
Sulfonylurea derivatives, thiazolidinediones	866 (0.3)
Oral antidiabetic + insulin	2,066 (0.7)
Triple therapy	2,924 (1.0)
Concomitant medication	
Antibiotics (J01)	5,072 (1.7)
Immunosuppressants (L04)	2,013 (0.7)
Corticosteroids for systemic use (H02)	4,527 (1.5)

All data except patient age are shown as number (%).

Table 2 reports the RORs of infections (overall) per antidiabetic drug compared with biguanides. The use of DPP-4 inhibitors as monotherapy (ROR 2.3 [95% CI 1.9–2.7]), insulins as monotherapy (ROR

**Table 2—Crude and adjusted RORs for any infection**

Drug	Reports (N)	Reports of infections (N)	ROR (95% CI)	
			Crude	Adjusted*
Biguanides	21,763	289	Reference	Reference
SU derivatives	16,675	258	1.2 (1.0–1.4)	1.1 (0.9–1.3)
TZDs	57,814	919	1.2 (1.1–1.4)	1.3 (1.1–1.5)
DPP-4 I	8,083	242	2.3 (1.9–2.7)	2.3 (1.9–2.9)
Insulins	80,347	1,703	1.6 (1.4–1.8)	1.5 (1.3–1.7)
OAD + OAD	11,991	155	1.0 (0.8–1.2)	0.9 (0.7–1.1)
OAD + insulin	2,066	48	1.8 (1.3–2.4)	1.5 (1.1–2.2)
≥3 ADs	2,924	39	1.0 (0.7–1.4)	1.1 (0.9–1.4)

ADs, antidiabetic drugs; DPP-4 I, dipeptidyl peptidase inhibitors; OAD, oral antidiabetic drug; SU, sulfonylurea; TZD, thiazolidinediones. \*Adjusted for age, sex, reporting year, reporting region, reporter type, and comedication affecting the immune system: antibiotics (J01), corticosteroids for systemic use (H02), and immunosuppressants (L04).

1.6 [95% CI 1.4–1.8]), and the combination of any oral antidiabetic drug and insulin therapy (ROR 1.8 [95% CI 1.3–2.4]) were all statistically significant associated with ADR reports of infections compared with biguanides. A slightly increased reporting of infections for patients using thiazolidinediones was found (ROR 1.2 [95% CI 1.1–1.4]), but no increased reporting of infections was found for sulfonylurea derivatives (ROR 1.2 [95% CI 1.0–1.4]), combination therapy of two oral antidiabetic drugs (ROR 1.0 [95% CI 0.8–1.2]), or for concomitant use of three or more antidiabetic drugs (ROR 1.0 [95% CI 0.7–1.4]). Adjustment for the potential confounding factors did not affect the results.

Assessment of different types of infections (Table 3) showed an increased reporting of URTI (ROR 12.3 [95% CI 8.6–17.5]) for the DPP-4 inhibitors, whereas the reporting for LRTI, UTI, and other infections was not increased. In addition, an increased reporting of URTI was found for users of thiazolidinediones (ROR 2.3 [95% CI 1.7–3.3]), and for concomitant use of three or more antidiabetic drugs (ROR 2.5 [95% CI 1.3–4.7]). Slightly increased RORs were found for the use of insulin monotherapy and the reporting of URTI (ROR 1.5 [95% CI 1.1–2.2]) and UTI (ROR 1.7 [95% CI 1.1–2.5]). The reporting of LRTI (ROR 1.8 [95% CI 1.4–2.3]) and other infections (ROR 1.7 [95% CI 1.4–2.0]) was also increased for insulin monotherapy. For the combination of an oral antidiabetic drug and insulin, increased reporting of UTI (ROR 3.5 [95% CI 1.7–7.2]) and other infections (ROR 1.7 [95% CI 1.1–2.6]) was noted. The other associations between antidiabetic drugs and infections were nonsignificant (Table 3).

The crude ROR was lower for DPP-4 inhibitors but was still significantly increased (ROR 1.6 [95% CI 1.3–1.9]) in the analysis of the data on the level of case reports. The RORs for other antidiabetic drugs did not change, except for insulin. The ROR for insulin monotherapy increased to 2.1 (95% CI 0.8–2.4). The sensitivity analyses showed that the country from which the case reports originates and the type of reporter did not have a major effect on the results (data not shown). The point estimates changed only slightly, but because of the decreased numbers the confidence intervals became wider.

**CONCLUSIONS**—This study showed that infections were approximately two times more frequently reported for DPP-4 inhibitors compared with biguanides in the WHO Vigibase. In particular, URTIs, including nasopharyngitis and sinusitis, were reported more frequently for DPP-4 inhibitors, although the reporting of URTI was also increased for users of thiazolidinediones, insulin monotherapy, and concomitant use of three or more antidiabetic drugs, but to a much lesser extent than for the DPP-4 inhibitors.

A hypothesis resulting from the current study is that the effect of DPP-4 inhibitors results in a slight imbalance of the immune system that causes an increased risk of common, less severe infections such as (viral) upper respiratory infections. This is supported by the results of the pivotal randomized clinical trials that also reported increased numbers of common infections rather than serious infections (1–3). As far as we are aware, no studies reporting serious infections in association with the use of DPP-4 inhibitors have been reported. At this

Table 3—Crude RORs for specific infections

Drug	URTI		LRTI		UTI		Other infections	
	N	ROR (95% CI)	N	ROR (95% CI)	N	ROR (95% CI)	N	ROR (95% CI)
Biguanides	38	Reference	65	Reference	30	Reference	166	Reference
SU derivatives	35	1.2 (0.8–1.9)	58	1.2 (0.8–1.7)	35	1.5 (0.9–2.5)	141	1.1 (0.9–1.4)
TZDs	233	2.3 (1.7–3.3)	232	1.4 (1.0–1.8)	113	1.4 (1.0–2.1)	367	0.8 (0.7–1.0)
DPP-4 I	171	12.3 (8.6–17.5)	20	0.8 (0.5–1.4)	13	1.2 (0.6–2.3)	51	0.8 (0.6–1.2)
Insulins	215	1.5 (1.1–2.2)	425	1.8 (1.4–2.3)	186	1.7 (1.1–2.5)	1,015	1.7 (1.4–2.0)
OAD + OAD	33	1.6 (1.0–2.5)	33	0.9 (0.6–1.4)	29	1.7 (1.0–2.9)	65	0.7 (0.5–0.9)
OAD + insulin	4	1.1 (0.4–3.1)	8	1.3 (0.6–2.7)	10	3.5 (1.7–7.2)	27	1.7 (1.1–2.6)
≥3 ADs	13	2.5 (1.3–4.7)	8	0.9 (0.4–1.9)	6	1.5 (0.6–3.6)	16	0.7 (0.4–1.2)

ADs, antidiabetic drugs; DPP-4 I, dipeptidyl peptidase inhibitors; OAD, oral antidiabetic drug; SU, sulfonylurea; TZDs, thiazolidinediones.

time, the magnitude of the effects of DPP-4 inhibitors on the immune system may not be compared with the magnitude of the effects as seen, for example, with biologic agents, resulting in rather serious infections such as tuberculosis or histoplasmosis due to tumor necrosis factor- $\alpha$  antagonists (19,20). With the current data, however, it was not possible to further differentiate between infections of different nature and viral, bacterial, or fungal causes.

The strength of this study is that the WHO VigiBase allows studying the association between use of antidiabetic drugs and infections outside the highly controlled environment of clinical trials. Nevertheless, some limitations of this study need to be addressed:

First, besides the known issue of underreporting in spontaneous reporting systems (21), the reporting pattern of ADRs may differ between new and old drugs, with the most vigorous monitoring at the time of marketing and shortly thereafter, as described by Weber (21). The DPP-4 inhibitors and thiazolidinediones were introduced in the study period (1999 through 2009), which might explain the relatively large number of reports for those drugs. However, it is unknown whether the type of ADRs that are reported changes over time and how this affects the results of this study. Nonetheless, adjustment for year of reporting did not affect the results.

Second, the results of this study may be subject to reporting bias, because infections are listed in both the EU and U.S. Summaries of Product Characteristics for all three DPP-4 inhibitors. This may have led to differential monitoring and reporting of infections for the DPP-4 inhibitors compared with other antidiabetic drugs. Increased reporting (physicians report ADRs that are likely to occur)

or decreased reporting (physicians do not report ADRs that are already mentioned in Summaries of Product Characteristics) might have occurred. In absolute terms, the number of reported infections is low: only 3% of the cases for DPP-4 inhibitors reports involved an infection (242 reports of infection of 8,083 case reports).

Furthermore, differences in classification strategies or misclassification may have occurred by the translation from clinical terminology to the classification systems used by the WHO VigiBase (WHO-ART or MedDRA terms). We do not expect, however, that this misclassification is different for different antidiabetic medicines, and the effect of this nondifferential misclassification on the results of this study will therefore be limited. In several case reports, more than one infection term was recorded, mainly consisting of a specific infection term (e.g., nasopharyngitis) and an a-specific term (e.g., URTI), which might influence the results. However, our analysis at the case-report level showed that the overall results did not change.

Unfortunately, we were not able to analyze the risk of infections for combination therapy on an individual drug-drug combination level owing to the low number of cases reporting each possible combination therapy. This is probably because comedication is only poorly reported in most case reports.

Finally, we reasoned that the different indications for the DPP-4 inhibitors in the U.S. versus the rest of the world, and a possible effect of the type of reporter (health care professional, consumer, or industry) on the case reports, might have influenced the results of this study. However, excluding reports from the U.S. and excluding reporting from consumers and industry did not affect the results.

Another explanation for our results can be that diabetes itself, and its progression, are often associated with an increased risk of infections. Although the literature is not yet conclusive on this, we could not exclude this possible association; therefore, the current study was limited to case reports of antidiabetic medicines only, thereby eliminating the effect of the disease itself. Some studies, however, suggest that more severe diabetes itself is also associated with higher risk of infections (14,22), although this is not supported by strong evidence. Because disease severity is therefore possibly associated with both exposure and outcome, this can be a confounding factor.

DPP-4 inhibitors are indicated as a second- or third-line therapy in combination with other oral antidiabetic drugs according to treatment guidelines in different parts of the world (23,24). Therefore, patients who are treated with DPP-4 inhibitors may in general be more severely ill compared with patients being treated with, for example, biguanides or sulfonylurea derivatives. In the current study, however, most of the case reports indicated a DPP-4 inhibitor was the only antidiabetic drug, which indicates monotherapy with DPP-4 inhibitors. A question prompted by this study is whether the patients treated with DPP-4 inhibitors monotherapy were indeed the more severely ill patients, because one antidiabetic drug was sufficient for these patients. In addition, for users of a combination of an oral antidiabetic and insulin or combination therapy of two antidiabetics (i.e., usually the more severely ill patients), we did not find an increased risk of infections. This is in line with the studies that did not find an association between diabetes mellitus and infection.

Besides infections in general, the association between diabetes and UTI has also been described (12,14,15,22), although we did not find significantly increased reporting of ADRs for UTIs and use of any of the antidiabetic drugs. Only for combination therapy of an oral antidiabetic and insulin did we find a slightly increased reporting for UTI. Channeling of this combination therapy toward the more severely ill diabetes patients, for which the use of insulin combined with an oral antidiabetic drug is a marker (25), may possibly explain this finding. This is in line with studies suggesting that the severity of the disease may play a role in the occurrence of UTI (14,22). Unfortunately, the subset of the Vigibase used in this study did not contain information on the severity of the underlying disease, so the effect of this phenomenon in the current study remains unclear.

Postmarketing evaluation of safety concerns raised during the preregistration phase of medicines is important for the assessment of the benefit-risk balance of drugs. This study adds to the knowledge of this specific safety issue for the DPP-4 inhibitors. The results of the study, using data reported to National Pharmacovigilance Centres, are in line with the findings from the clinical trial program that included a much more selected patient population. However, more research is needed to further evaluate the clinical and regulatory consequences of this finding, such as severity of the infections.

As a result of the observed increased risk in RCTs, the Risk Management Plans for DPP-4 inhibitors also address a possible increased risk of infections. The definition of the outcome ("infection") in the postauthorization safety studies that are being conducted as part of the Risk Management Plans is, therefore, of particular importance. Because our study points out that several types of infections (URTIs such as sinusitis and nasopharyngitis) are more frequently reported than others, the outcome should not be limited to infections in general but should also take specific types of infections into account. In addition, the nonserious infections seem to be neglected in the postauthorization safety studies because all studies aim to investigate the risk of serious infections (1–3). Although from a regulatory viewpoint the focus on serious infections is understandable, the effect of (recurrent) nonserious infections on the quality of life can also be considerable.

In conclusion, the results of this study show that there is an increased reporting of infections for users of DPP-4 inhibitors compared with users of other antidiabetic drugs. Although the limitations of spontaneous reporting systems (e.g., underreporting, the Weber effect, reporting bias) should be taken into account, physicians and patients nevertheless should remain vigilant on the occurrence of infections and continue to report infections as possible ADRs. Infections may be related to diabetes, but a direct effect of the medication on the occurrence of infections should be considered.

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