

BRIEF REPORT

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Safety and effectiveness of linagliptin in Korean patients with type 2 diabetes: A postmarketing surveillance study

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Abstract

We designed a postmarketing surveillance study of linagliptin for patients with type 2 diabetes (T2D) in Korea. This prospective, observational, multicentre study investigated the safety and glycaemic effectiveness of linagliptin as monotherapy or combination therapy with other antidiabetic drugs in routine clinical practice. Endpoints were the incidence of adverse drug reactions (ADRs) and the change in HbA1c. Overall, 3119 and 2171 patients were included in the safety and effectiveness analysis sets, respectively. A total of 56 patients (1.8%) experienced ADRs. The most common ADR was gastrointestinal disorders (0.7%), followed by metabolism and nutrition disorders (0.5%). ADRs of special interest, including pancreatic diseases, cardiac diseases and hypoglycaemia, occurred in 12 patients, 11 of whom had hypoglycaemia, while one had a skin lesion. Mean HbA1c change during the study period was -0.8% . Lower body mass index, shorter diabetes duration and higher baseline HbA1c were independently associated with a better effectiveness, while the presence of diabetic complications, dyslipidaemia and the use of sulphonylureas were associated with a poor response. In conclusion, linagliptin showed an excellent safety profile and glycaemic effectiveness in Korean patients with T2D.

KEYWORDS

antidiabetic drug, linagliptin

1 | INTRODUCTION

Dipeptidyl peptidase-4 (DPP-4) inhibitors improve blood glucose levels by preventing rapid degradation of incretin hormones, which increase postprandial insulin secretion and inhibit glucagon from pancreas.¹ Linagliptin, a xanthine-based DPP-4 inhibitor, received approval from the United States Food and Drug Administration for clinical treatment of type 2 diabetes (T2D) in 2011 and was approved by the Korean Ministry of Food and Drug Safety (MFDS) the same year. The glycaemic efficacy and safety of linagliptin has been reported in a number of clinical studies.^{2–5}

However, studies of the safety and effectiveness of linagliptin in routine clinical practice are still insufficient, especially in Korea. Therefore, the present postmarketing surveillance (PMS) study was designed to investigate the safety and effectiveness of linagliptin in routine clinical settings for Korean patients with T2D.

2 | MATERIALS AND METHODS

2.1 | Study design

This non-comparative, prospective, observational, open-label PMS study (ClinicalTrials.gov, NCT01707147) investigated the safety and effectiveness of linagliptin (Trajenta 5 mg; Boehringer Ingelheim International GmbH & Co., Ingelheim, Germany). Patients with T2D were recruited from 64 institutions in Korea and received linagliptin 5 mg once daily as monotherapy or as combination therapy with other anti-diabetic drugs (ADDs) from 14 September 2011 to 13 September 2017 (6 years).

Enrolled patients were followed for a 24-week treatment period or until linagliptin discontinuation. Previous ADDs except for linagliptin were maintained, titrated or switched in accordance with the physician's decision during the study period. Lifestyle modification therapy and education on both diet and exercise were also provided in parallel with the medications.

The primary endpoint of the study was the incidence of adverse drug reactions (ADRs), which were collected using the *Medical Dictionary for Regulatory Activities*, version 20.0. If the ADR was life-threatening or the outcome of it was death, hospitalization, disability or permanent damage, it was defined as a serious ADR. ADRs related to hepatobiliary diseases, pancreatic diseases, skin disorders, cardiac symptoms and hypoglycaemia were classified as 'ADRs of special interest'.

The effectiveness of linagliptin was assessed by comparing changes in fasting plasma glucose (FPG) level and HbA1c between the initial and the final observation dates. Clinical data including demographic characteristics, baseline vital signs and medical history were assessed and recorded in electronic case report forms at the first visit. Blood samples were obtained to measure HbA1c and FPG.

This study was conducted in accordance with the *Basic Standards for the Re-examination of New Medicines*, published by the Korean

MFDS. The follow-up period was also determined according to the guidelines. All institutions received ethical approval from their institutional review boards according to the rules of each institution. Informed consent was obtained from all the patients participating in this study.

2.2 | Statistical analysis

Continuous variables are expressed as means $\pm$ standard deviations, and categorical variables are shown as numbers and percentages. For the subgroup analysis of safety results, a chi-squared test was used to compare the incidence of ADRs between subgroups. As presented in the Results section, the incidence of ADRs was very low; therefore, we did not perform regression analysis. In the effectiveness analysis, changes in HbA1c and FPG levels between the baseline and final observation were compared using a paired t-test. Student's t-test or one-way ANOVA followed by Bonferroni's post hoc test were used to compare the effectiveness of linagliptin use between the subgroups. Multiple linear regression analysis was performed to identify independent variables that were significantly correlated with the change in HbA1c. All statistical analyses were performed using SAS software (SAS Institute Inc., Cary, NC, USA) version 9.4, and results with $p < .05$ were considered statistically significant.

3 | RESULTS

3.1 | Study population characteristics

A total of 3219 subjects were initially collected from 64 institutions in Korea (Figure S1), 3119 of whom were included in the safety analysis, and 2171 in the effectiveness analysis. The baseline characteristics of the participants in the safety analysis set are presented in Table S1. The mean age of patients was 61 years, and the mean duration of diabetes was approximately 8 years. Baseline HbA1c, FPG level and estimated glomerular filtration rate were 8.0%, 163.4 mg/dL and 72.8 mL/min/1.73 m², respectively. In total, 91.7% of patients received concomitant ADDs with linagliptin. The mean linagliptin administration period was 172.4 days. Three hundred and ninety-one patients (12.5%) prematurely terminated the study. The reasons for premature withdrawal were adverse events ($n = 38$, 1.2%), loss to follow-up ($n = 220$, 7.1%), and others ($n = 133$, 4.3%) such as prescription change, drop-out and withdrawal of consent.

3.2 | Safety results for linagliptin

The incidences of ADRs by system organ class for linagliptin are presented in Table S2 and Figure 1. A total of 56 patients (1.8%) reported ADRs. The most common ADR was gastrointestinal disorder ($n = 21$, 0.7%), followed by metabolism and nutrition disorders ($n = 14$, 0.5%) then nervous system

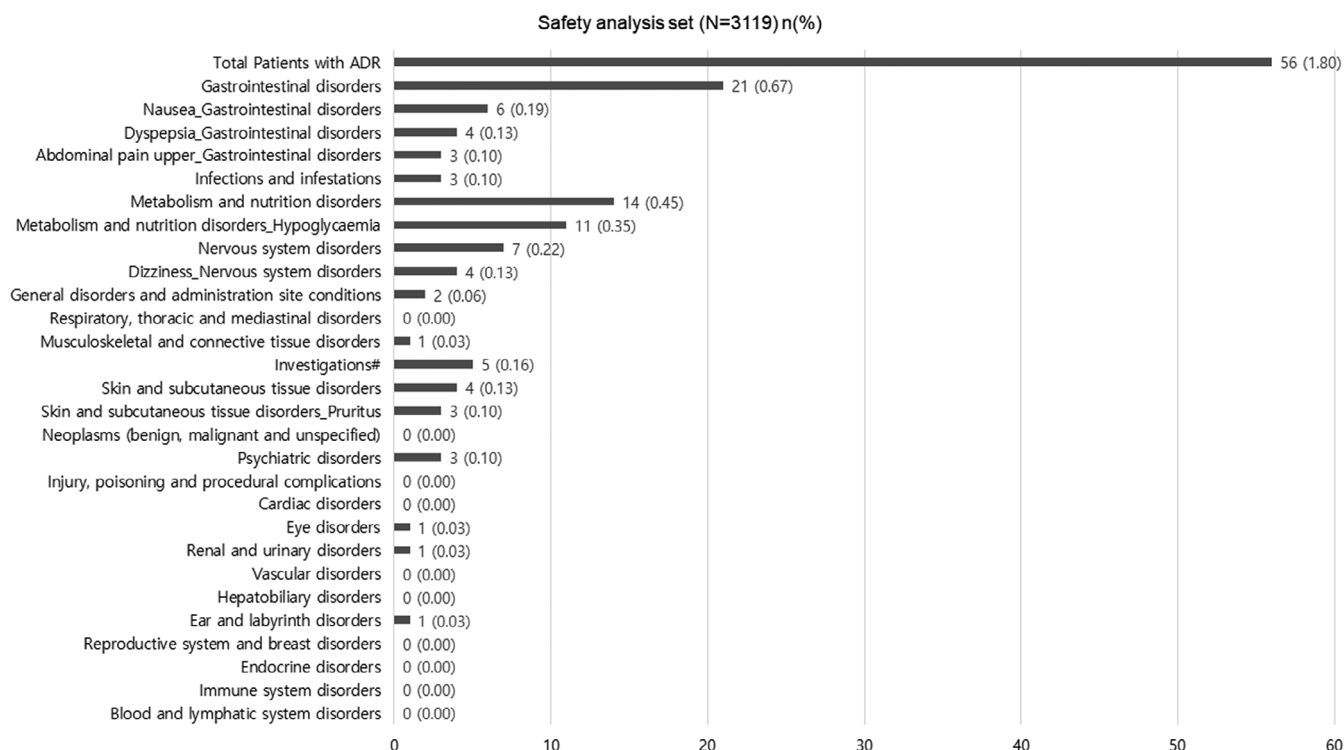


FIGURE 1 Number of patients with an adverse drug reaction. Presented as number (%). #Composed of two subjects with elevated alanine aminotransferase (ALT), two subjects with weight decrease and one subject with blood triglyceride elevation. ADR, adverse drug reaction

disorders ($n = 7$, 0.2%). In subgroup analysis, ADRs tended to be higher in females, non-smokers and patients without hypertension or kidney diseases (Table S3). However, these trends should be interpreted while taking into consideration the low number of overall ADRs. A total of six serious ADRs were noted in three subjects (Table S4), and two fatal adverse events were noted. The fatal adverse events were one case of mortality, which was beyond the scope of the investigation, and one case of cardiac arrest after oedema and respiratory symptoms. Investigators assessed the causal relationship between these cases and the administration of linagliptin as being improbable.

A total of 12 patients had ADRs of special interest (Table S5), 11 of whom had hypoglycaemia, while one had a mild skin lesion. Among 11 patients who had hypoglycaemia, 10 received a sulphonylurea with linagliptin. Only one patient developed mild hypoglycaemia while receiving linagliptin monotherapy. There were no patients with hepatobiliary diseases, pancreatic diseases or symptoms related to cardiac diseases.

3.3 | Effectiveness of linagliptin use

Baseline characteristics of the patients in the effectiveness analysis set were similar to those in the safety analysis set (Table S6). The mean change in HbA1c during the study period was -0.8% (Table S7) and this change was statistically significant ($p < .001$). In the subgroup analysis, the effect of linagliptin use on HbA1c reduction was

significantly better in those patients who were younger than 65 years; patients with a diabetes duration of less than 4 years; patients without diabetes complications, hypertension, dyslipidaemia or coronary artery disease; and patients with normal kidney function (Table S8). Multiple regression analysis showed that lower body mass index (BMI), shorter diabetes duration and higher baseline HbA1c were independently associated with a better effectiveness, whereas the presence of diabetic complications, dyslipidaemia and the use of sulphonylureas were associated with a poor glycaemic response in patients receiving linagliptin (Table 1).

4 | DISCUSSION

In this PMS study, the incidence of overall ADRs was 1.8%. The most common ADR was gastrointestinal disorders (0.7%), followed by metabolism and nutrition disorders (0.5%) then nervous system disorders (0.2%). Only six serious ADRs, which occurred in three subjects (0.1%), were noted, and all three subjects recovered after proper management. In the ADRs of special interest, including pancreaticobiliary disease, cardiovascular disease and hypoglycaemia, only 11 cases of hypoglycaemia and one case of skin disorder were reported. There were no ADRs related to pancreaticobiliary diseases during the study period, which is consistent with the result of a previous pooled analysis of linagliptin.⁶ In addition, there were no ADRs associated with

TABLE 1 Multiple regression analysis of factors associated with the change in HbA1c

	Change in HbA1c ^a	
	β	<i>p</i> -value
Age	−0.003	.34
Sex; male (0) or female (1)	−0.12	.07
BMI (mg/kg ²)	0.02	<.001
Duration of diabetes	0.03	<.001
Presence of diabetic complications	0.2	.006
Presence of hypertension	−0.08	.33
Presence of dyslipidaemia	0.23	.001
Presence of coronary artery disease	0.12	.16
Baseline HbA1c (%)	−0.66	<.001
eGFR (mL/min/1.73 m ²)	−0.001	.38
Use of metformin	−0.11	.13
Use of sulphonylurea	0.32	<.001

Abbreviations: β , regression coefficient; BMI, body mass index; eGFR, estimated glomerular filtration rate.

^aChange in HbA1c from baseline to the final observation date; negative values indicate decrease in HbA1c.

cardiovascular disease, which is in line with the results of previous studies.^{7,8}

Compared with previous studies conducted in Asia, the incidence of overall ADRs was considerably lower; the incidence of ADRs in a PMS study of linagliptin monotherapy in Japan that followed up for an average of 115 weeks was 10.7%,⁹ and in a 114-week PMS study of linagliptin combination therapy the incidence was 11.4%.¹⁰ In phase 3 studies, the incidence of ADRs in a 52-week study in Japan was 10.2%,¹¹ whereas it was 3.0% in a 24-week multinational trial of Asian patients.¹² However, in a 52-week PMS study of vildagliptin, another type of DPP-4 inhibitor, the incidence of ADRs was 1.4%, similar to our study.¹³

There were also some differences regarding the composition of ADRs between this study and previous studies. While metabolism disorders, mainly uncontrolled T2D, were the dominant ADRs in previous PMS studies of linagliptin,^{9,10} gastrointestinal disorders were the most common in our study, and most of the metabolism disorders were cases of hypoglycaemia. However, in those previous studies, gastrointestinal disorder was also one of the most frequent ADRs. Furthermore, in the PMS studies of other DPP-4 inhibitors such as sitagliptin, vildagliptin and teneligliptin, hypoglycaemia and gastrointestinal disorders were the major ADRs.^{13–15}

We assumed that the shorter observation period in the current PMS study (24 weeks) was a reason for the comparatively low incidence of ADRs, and the different composition of the ADRs. When we analysed patients treated with linagliptin monotherapy separately, there was no significant difference in the incidence of ADRs compared with the combination group, which was consistent with previous PMS studies^{9,10} (data not shown).

In terms of effectiveness, the current study confirmed the glucose-lowering effects of linagliptin use in Korean patients with T2D in a real-world setting. The mean changes in HbA1c were similar to the results of the Japanese PMS studies,^{9,10} a pooled analysis of data from Asian patients,¹⁶ and PMS studies of other DPP-4 inhibitors.^{13–15} Our subgroup analysis also revealed that blood glucose levels were effectively reduced in all linagliptin-treated patients categorized by various clinical factors. However, the glucose-lowering effects were more pronounced in patients with a shorter duration of T2D, lower BMI values, higher baseline HbA1c, no history of diabetic complications, no history of dyslipidaemia, and in those not using sulphonylureas at all. The result that the glucose-lowering effect of linagliptin use was not affected by age is in line with that of previous studies, but the association between hypoglycaemic effect and BMI differed from that observed in previous studies.^{9,16}

This study has several limitations. First, the follow-up period was short compared with previous PMS studies in other Asian countries, as mentioned above. Therefore, the incidence of ADRs might have been underestimated in this study. Second, because of the low number of ADR cases, statistically meaningful regression analysis could not be performed in the subgroup analysis of safety results. Finally, because of the observational nature of PMS studies, the possibility that other unidentified confounding factors influenced the subgroup analyses cannot be excluded. Despite these limitations, the current PMS study is important as it provides clinical evidence regarding the safety and effectiveness of linagliptin in Korean patients with T2D in a real-world setting. To our knowledge, this is the first PMS report of linagliptin in Korean patients. In addition, we conducted regression analysis to find independent variables that were significantly correlated with the effectiveness of linagliptin, which was not performed in previous PMS studies.

In conclusion, this study provides data on the safety and effectiveness of linagliptin use among Korean patients with T2D in routine clinical settings. Linagliptin showed excellent safety, without any cases of pancreaticobiliary or cardiovascular diseases. Furthermore, linagliptin effectively lowered blood glucose levels, which is consistent with the results of previous studies.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

E.S.K designed and supervised the study. All authors conducted the study and contributed toward data acquisition. J.B drafted and revised the manuscript for important intellectual content and interpreted the data. All authors reviewed and approved the final manuscript.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/dom.14317>.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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