ISSN: 0975-3583,0976-2833 VOL14, ISSUE 05, 2023

Treatment With Evogliptin for Type 2 Diabetes Effectiveness and Safety

Kamran Khan, Diabetologist, Advanced Diabetes Care and Research Centre, Bhagalpur, Bihar, India

ABSTRACT:

Objective: To assess the effectiveness and safety of evogliptin versus linagliptin in type 2 diabetic patients.

Method: 200 individuals with type 2 diabetes with HbA1c levels between 7.1% and 10.1% were divided equally into two groups and given daily doses of either linagliptin 5 mg or evogliptin 5 mg for a period of 12 weeks. The change from baseline HbA1c at week 11 served as the primary efficacy outcome. The change in the mean amplitude of glycaemic excursion (MAGE), as determined by continuous glucose monitoring, served as the secondary endpoint. Evogliptin 5 mg daily was given to both groups in the extension study during the course of the subsequent 11 weeks: the evogliptin/evogliptin group (n = 100) and the linagliptin/evogliptin group (n = 100).

Results: The mean change in HbA1c in the linagliptin and evogliptin groups after 11 weeks of treatment was 0.84 and 0.74 percent, respectively. Based on a non-inferiority margin of 0.3%, the between-group difference was 0.11% (95% CI: -0.31 to 0.10), indicating noninferiority. In the evogliptin group, the change in MAGE was 24.5 mg/dL, whereas in the linagliptin group, it was 16.6 mg/dL. These numbers were significantly below the starting points in both groups' data. However, there was little difference between the two groups. At week 25, HbA1c decreased by 0.93% in the evogliptin/evogliptin group, with HbA1c values of 7.1% in 80.1% of the patients. For 25 weeks, there was no significant difference in the frequency or kind of adverse events between the two groups.

Conclusion: Evogliptin's ability to reduce blood sugar in this study was non-inferior to linagliptin's. A 0.93% decrease in HbA1c at week 25 allowed for its maintenance. In patients with type 2 diabetes, evogliptin medication increased glycaemic variability without resulting in any severe side effects.

Keywords: Type 2 Diabetes, Evogliptin, Glycemic, Linagliptin, HbA1c

INTRODUCTION:

In diabetic patients, glycemic management has been viewed as lowering the average blood glucose level through regulating HbA1c. However, HbA1c does not account for inter-person variations in blood glucose levels and has poor prognostication of the risk of hypoglycemia, which is the primary barrier to intensive diabetes treatment [**Figure 1;** 1]. Currently, reducing glycaemic variability, which is caused by postprandial hyperglycemia and treatment-related hypoglycemia, has replaced lowering HbA1c levels as one of the main therapeutic objectives in the management of diabetes [2].

ISSN: 0975-3583,0976-2833 VOL14, ISSUE 05, 2023

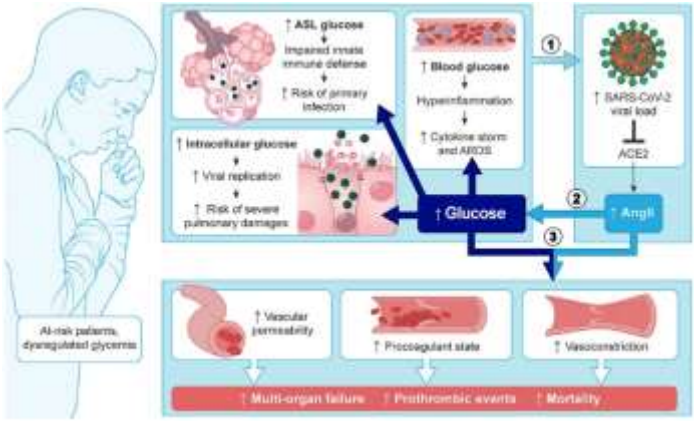

Figure 1: Role of HbA1c

Nowadays, continuous glucose monitoring (CGM) is regarded as a reliable technique for determining glycaemic variability.4 Increased glycaemic variability as measured by CGM has been linked to diabetic sequelae like diabetic retinopathy, cardiovascular problems, and death, according to a number of studies [3]. Additionally, elevated glycaemic variability is closely linked to oxidative stress, which can lead to the emergence of cardiovascular disease [4]. Dipeptidyl peptidase-4 (DPP-4) inhibitors are frequently used as first-line treatments for patients who cannot tolerate metformin or as second-line treatments after metformin for people with type 2 diabetes (T2D) [5]. DPP-4 inhibitors based on incretin have a minimal risk of causing hypoglycemia. They have no impact on body weight and can enhance -cell function. They also significantly and clinically meaningfully reduce blood sugar [6]. According to a recent study, DPP-4 inhibitors were linked, in a glucose-dependent way, to less changes in blood glucose levels in both hypoglycemic and hyperglycemic status [7]. Within 60 minutes, evogliptin was shown to inhibit >80% of plasma DPP-4 activity, and the inhibitory effect persisted for 24 hours [8]. When compared to placebo, evogliptin increased postprandial active glucagon-like peptide-1 (GLP-1) levels by 1.5 to 2.4-fold, lowering postprandial glucose levels by 20% to 35%. Evogliptin is not metabolised by the kidneys, hence dose modifications are not necessary in patients with renal impairment [9]. Within 60 minutes, evogliptin was shown to inhibit >80% of plasma DPP-4 activity, and the inhibitory effect persisted for 24 hours [8]. When compared to placebo, evogliptin increased postprandial active glucagon-like peptide-1 (GLP-1) levels by 1.5 to 2.4-fold, lowering postprandial glucose levels by 20% to 35%. Evogliptin is not metabolised by the kidneys, hence dose modifications are not necessary in patients with renal impairment [9]. In preclinical trials, evogliptin also had positive effects on the kidneys, including decreases in albuminuria and the attenuation of renal fibrosis [10].

We predicted that evogliptin, a new DPP-4 inhibitor, would have strong glucose-lowering effects through reducing glucose fluctuation and tolerance with a low risk of adverse events (AEs). This was based on these findings. Another DPP-4 inhibitor, linagliptin, is primarily excreted into the gastrointestinal tract through bile (85%), with only 6% of its excretion occurring through the kidneys. As a result, patients with renal impairment do not need to have their doses adjusted [11]. The goal of this study was to compare the efficacy and safety of evogliptin with linagliptin

ISSN: 0975-3583,0976-2833 VOL14, ISSUE 05, 2023

as an active comparator, showing changes in HbA1c, CGM, and renal variables for 12 weeks and an extension period of 12 weeks in inadequately controlled patients with T2D. Linagliptin has been shown to have positive effects on glycaemic variability and renal outcomes in addition to its glucose-lowering effects.

METHODS:

Study Design: This was a prospective study carried out at Advanced Diabetes Care and Research Centre, Bhagalpur within one year of study.

Methodology: The individuals were given evogliptin and linagliptin placebos in a single-blind fashion for 15 days starting on the day of visit 2 until the day before visit 2 to those who met the inclusion criteria at visit 1 (week 1). Depending on whether their HbA1c in the clinical laboratory test results from visit 1 was 7% or 7%, the participants were randomly assigned at visit 3 (week 1) to either receive evogliptin 5 mg and linagliptin placebo (evogliptin group) or evogliptin placebo and linagliptin 5 mg (linagliptin group) in a double-blind manner for 11 weeks. A CGM device was attached to the individual for 2 days during visits 2 (two days before visit 3), and 5 (two days before visit 6). In the extension period, evogliptin 5 mg was given open label to both groups (evogliptin/evogliptin and linagliptin/evogliptin) for 11 weeks, from the day of visit 6 (week 11) to the day before visit 9 (week 23). During visit 8 (two days prior to visit 9), the subject had a CGM device on for two days. The CGM device was removed from the individual during visit 9 (week 23).

Subjects with fasting plasma glucose (FPG) values of >170 mg/dL at visits 3, 4, and 6 were allowed to receive metformin as a rescue therapy, as were subjects with FPG >140 mg/dL at visits 7 and 9, as well as any other subjects the investigator felt required to receive a rescue medication.

The change in the mean level of HbA1c from baseline to 11 weeks after treatment with evogliptin or linagliptin was the study's main effectiveness objective. The proportions of patients with HbA1c of 6.0% or 7.5% at 11 weeks, changes in FPG from baseline to 11 weeks after therapy, and the CGM variables at 11 and 25 weeks were the secondary efficacy objectives. Changes in the mean amplitude of glucose excursions (MAGE), the coefficient of variance (CV), the standard deviation (SD), and the mean of daily differences (MODD) were used to measure intra-day and inter-day variability using the CGM system. Major intra-day glucose swings can be estimated using the MAGE variable, but minor ones are not taken into account. This variable, which was larger than one SD from the mean value, was calculated as the arithmetic average of the absolute value variations between successive glucose peaks and nadirs. The CV, which describes the range of the glucose readings, was defined as the ratio of SD to the mean. For assessing the degree of variation in subjects with various mean glucose levels, the variation within them is helpful. The MODD, which was derived as the mean of the absolute value differences between the glucose levels taken at the same time of day on two consecutive days, is the only indicator for evaluating the day-to-day glycaemic variability.

Nitrotyrosine and 2-thiobarbituric acid-reactive substances (TBARS), which are indicators of oxidative stress and inflammation, were among the exploratory endpoints. Nephrin, a test for

ISSN: 0975-3583,0976-2833 VOL14, ISSUE 05, 2023

podocyte injury, and N-acetyl-D-glucosaminidase (NAG), a sign for proximal tubular damage, were also assessed. At baseline and 11 and 25 weeks following treatment, biochemical factors such as creatinine, the estimated glomerular filtration rate (eGFR), and the urine albumin-to-creatinine ratio (UACR) were measured. During the course of the study, AEs, serious AEs (SAEs), and adverse drug reactions (ADRs) were noted. At baseline and 11 and 25 weeks after treatment, lipid parameters (total cholesterol, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, and triglycerides) and liver enzymes (aspartate aminotransaminase [AST] and alanine aminotransaminase [ALT]) were assessed.

Sample Size: 210 patients were originally enrolled in this study, bit after meeting the inclusion criteria, only 200 patients were enrolled.

Inclusion criteria: Patients are required to be over 21 years old, diagnosed with T2D, have an HbA1c level between 7.1% and 10.1%, have a body mass index (BMI) between 21 and 41 kg/m2, and had not recently received a prescription for a hypoglycemic drug.

Statistical analysis: Categorical variables are reported as frequencies with percentages, whereas all continuous variables are presented as means SDs. Depending on the level of normality satisfaction, either a paired t-test or a Wilcoxon signed-rank test was used to compare the data from the treatment groups' baseline, week 11 and week 25 findings. For comparisons between the two groups, categorical data were subjected to either a Chi-squared test or a Fisher's exact test, depending on the situation, and continuous efficacy factors were subjected to either a two-sample t-test or a Wilcoxon rank-sum test. We also conducted subgroup analyses based on HbA1c (>7.0%, <7.0%). In general, SAS version 9.4's two-sided test with a significance level of 4% was used for all statistical analyses.

RESULTS:

Randomization was used to assign 100 patients each to the linagliptin and evogliptin groups. 95 (93%) of the evogliptin-treated patients and 97 (92%) of the linagliptin-treated patients successfully completed the 11-week main study. As the evogliptin/evogliptin group and the linagliptin/evogliptin group, respectively, 94 patients in the evogliptin 5 mg group and 91 patients in the linagliptin 5 mg group took part in the extension trial. Finally, the 11-week extension trial was successfully completed by 91 patients (91%) in the evogliptin/evogliptin group and 87 patients (83%) in the linagliptin/evogliptin group.

Table 1 provides a summary of the demographic and clinical features of the randomised individuals at baseline. 114 (55.5%) of the study's subjects were men, with a mean age of 56.2±10.3 years. In both groups, the mean baseline HbA1c level was 7.81% and the mean baseline BMI was 26.0±3.3 kg/m2. Between the two groups, the baseline characteristics did not significantly differ. During the 11-week main study, there was no statistically significant difference in the number of subjects who received rescue medications at least once between the two treatment groups: 1 (1%) in the evogliptin group and 2 (2.8%) in the linagliptin group (P = 0.246).

ISSN: 0975-3583,0976-2833 VOL14, ISSUE 05, 2023

TABLE 1: BASELINE CHARACTERISTIC OF PATIENTS

Criteria	Evogliptin (n = 100)	Linagliptin (n = 100)	P-value
Age [yrs]	56.5 (10.6)	55.5 (10.1)	0.691
Gender [female; %]	59.7%	51.3%	0.224
BMI (kg/m^2)	26.1 (3.2)	26.1 (3.4)	0.558
Obesity (%)	57.7%	57.2%	0.918
Duration of diabetes (years)	4.0 (4.3)	3.6 (4.0)	0.565
Duration of diabetes ≤3 weeks, (%)	25.4%	21.8%	0.543

For the evogliptin group, the change in HbA1c from the baseline to week 11 was 0.84% 0.66% and for the linagliptin group, it was 0.74%±0.86%. At week 11, both the evogliptin and the linagliptin groups showed a significant decline from the baseline HbA1c (both P <0.0002). Since the between-group difference was less than the non-inferiority margin of 0.41% and the upper limit of the two-sided 95% CI was less than 0.10%, the evogliptin group was not inferior to the linagliptin group. Similar to the FA set, the between-group difference in HbA1c at week 11 in the PP set was 0.02% [95% CI: 0.24, 0.21]. The primary endpoint of this trial, the change in the mean HbA1c level from baseline to week 11, was examined using a mixed-effects model with repeated measures (MMRM) for sensitivity analysis. The fixed categorical effects of treatment, visit, and treatment-by-visit interaction were included in the MMRM. The between-group difference, which was comparable to that in the FA set, was determined to be 0.07% (95% CI: 0.31, 0.13).

In the extension research, the use of evogliptin caused the levels of HbA1c to drop steadily. In the evogliptin/evogliptin group, the change in HbA1c from baseline to week 24 was 0.93%±0.74% and 0.82%±0.4% in the linagliptin/evogliptin group. Following a 12-week course of treatment with linagliptin or evogliptin, the FPG fell by 12.7 ±19.4 mg/dL and 15.3±34.1 mg/dL, respectively (both P <0.0002). However, there was no discernible difference in the FPG values between the two treatment groups (P =0.324). There was no statistically significant difference between the groups (P = 0.161), although the PP set revealed significant changes in FPG of 12.7±18.7 mg/dL in the evogliptin group and 16.4±36.5 mg/dL in the linagliptin group. These outcomes matched those of the FA set quite closely. In the extension study, the difference in FPG between the evogliptin/evogliptin group and the lnagliptin/evogliptin group from baseline to week 25 was 11.6±25.0 mg/dL and 14.2±24.5 mg/dL, respectively (both P <0.0002).

The change in FPG from baseline to week 25 in the extension study was 11.6±25.0 mg/dL for the evogliptin/evogliptin group and 14.2±24.5 mg/dL for the lnagliptin/evogliptin group (both P <0.0002). In subgroup analysis, patients with HbA1c values of 7.0% and 7.0% showed substantial declines in HbA1c and FPG levels from baseline to week 11. In comparison to patients with HbA1c values of 7.0%, patients with HbA1c values of 8.0% experienced higher

ISSN: 0975-3583,0976-2833 VOL14, ISSUE 05, 2023

changes in HbA1c and FPG levels from baseline to week 11. However, there were no significant differences between the two groups.

After week 11 administrations, a comparable percentage of patients in each treatment group achieved HbA1c levels of 6.5%, according to the HbA1c target goal achievement rate. HbA1c levels of less than 6.5% were present in 43% of patients on evogliptin and 36.3% of patients taking linagliptin (P = 0.317 by Fisher's exact test). Without a significant difference between the groups (P = 2.000), 68.1% of the evogliptin group and 67.2% of the linagliptin group achieved this objective goal when a HbA1c of 7.1% was employed. The outcomes from the PP set were comparable to those from the FA set. Without any discernible between-group differences, 46.1% of the evogliptin group and 38.0% of the linagliptin group each attained a HbA1c of less than 6.5% (P = 0.291).

The HbA1c levels of 72 (80.2%) and 43 (48.3%) of the 90 participants in the evogliptin/evogliptin group in the extension phase were 7.0% and 6.5%, respectively. The HbA1c levels of 60 (70.8%) and 34 (40.6%) of the 85 participants in the linagliptin/evogliptin group were 7.0% and 6.5%, respectively. Similar numbers of participants in both groups had HbA1c readings of less than 6.5% or more than 7.0% at week 23. After 11 weeks of treatment, both groups' glycaemic variability values—including SD, MAGE, CV, and MODD—and mean glucose over 1 to 25 hours—significantly decreased. Results from the PP set were comparable. After 11 weeks of treatment, both groups' percentages of time spent between 60 and 170 mg/dL and their percentages of time spent in hyperglycemia (>170 and >240 mg/dL) were dramatically decreased. The percentage of time spent in the 60-170 mg/dL range increased in the evogliptin group from 67.6% at baseline to 81.5% at week 11 (P 0.0002), while the percentage of time spent in hyperglycemia (>170 mg/dL) reduced by 13.6% (P 0.0002) at week 11 from baseline. Similar outcomes were seen in the linagliptin group, hence there were no discernible variations in these CGM variables between the two groups.

At week 25, the mean daily glucose level measured by CGM decreased in the evogliptin/evogliptin group by 24.61±30.60 mg/dL and in the linagliptin/evogliptin group by 15.1±27.1 mg/dL (both P <0.0002). At week 25, the SD decreased in the evogliptin/evogliptin group by 10.28±11.90 mg/dL and in the linagliptin/evogliptin group by 6.61 10.77 mg/dL (both P <0.0002). In the same way, the evogliptin/evogliptin group's change in MAGE from baseline to week 24 in the extension study was 26.85±33.72 mg/dL (P< 0.0002) and the linagliptin/evogliptin group's change was 13.36±29.66 mg/dL (P = 0.0022). Patterns in the CV and MODD were comparable.

After the initial 11 weeks of treatment, neither group's eGFR or nephrin levels significantly changed. In the evogliptin/evogliptin group, the percentage change from baseline in the UACR at week 24 significantly dropped by 47.26± 262.23%, and in the linagliptin/evogliptin group, it decreased by 35.27± 258.84%. Only the evogliptin group showed substantial drops in urine NAG at weeks 12 (P = 0.0288) and 25 (P = 0.0025), while the inter-group difference was not statistically significant. At week 11, there was no significant difference between the two groups; however, the evogliptin group was the only one to show significantly greater reductions in

ISSN: 0975-3583,0976-2833 VOL14, ISSUE 05, 2023

nitrotyrosine and TBARS (both P <0.02). Regardless of the study drug's aetiology, 29.6% of evogliptin group patients and 40.1% of linagliptin group patients suffered adverse events after 11 weeks of therapy. 4.1% of those using evogliptin and 4.7% of those taking linagliptin both experienced ADRs.

During the 11-week main study period, three patients in the linagliptin group and three patients in the evogliptin group experienced SAEs. All SAEs were thought to be unrelated to the investigational product in any way. Severe hypoglycemia, asymptomatic hypoglycemia, documented symptomatic hypoglycemia, likely symptomatic hypoglycemia, and relative hypoglycemia were the categories used to classify the hypoglycemic occurrences. 27 patients (29.7%) in the evogliptin/evogliptin group and 25 participants (28.8%) in the linagliptin/evogliptin group experienced asymptomatic hypoglycemia. In the linagliptin/evogliptin group, documented symptomatic hypoglycemia occurred in 3 individuals (2.21%). In the evogliptin/evogliptin group, one participant (1.11%) experienced probable symptomatic hypoglycemia. 27 patients (29.7%) in the evogliptin/evogliptin group and 25 patients (28.8%) in the linagliptin/evogliptin group experienced total hypoglycemia.

At week 11, both groups' LDL cholesterol levels significantly dropped. Only the evogliptin group's AST and ALT levels considerably dropped at week 12, although there was no discernible between-group difference.

DISCUSSION:

In this randomised, double-blind, active-controlled, multicenter research that lasted 12 weeks, evogliptin medication significantly reduced HbA1c by 0.84% ± 0.66%, which was non-inferior to linagliptin treatment. The evogliptin group continued to show lower HbA1c levels after 25 weeks of therapy. At week 25, 80.1% of the subjects in the evogliptin group had HbA1c levels below 7.0%, which was the glycaemic target goal. The use of evogliptin also improved glycaemic variability, resulting in wider glucose goal ranges and shorter times between hypo- and hyperglycemia as measured by the CGM device. For the entire 25-week duration of the clinical trial, evogliptin was well tolerated. The glucose-lowering effectiveness of evogliptin was shown to be strong in the current investigation. At weeks 11 and 25, the HbA1c level dropped by 0.84% and 0.93%, respectively. The majority of the CGM indicators dramatically improved from baseline to week 25 whereas the FPG fell significantly over the course of the whole 24-week research period.

By raising GLP-1 levels, DPP-4 inhibitors are known to cause glucose-dependent insulin secretion and prevent the generation of glucagon [12]. In this way, evogliptin medication significantly lowered fasting and postprandial glucose levels without raising the danger of treatment-induced hypoglycemia. This was connected to evogliptin treatment's considerable reductions in glycaemic variability as measured by CGM. It should be noted that in this investigation, we investigated multiple glycaemic variability measures (SD, CV, MAGE, and MODD) that represent intra-day variation and daily variability assessed by CGM [13–15]. All of these glycaemic variability values in the evogliptin group demonstrated significant decreases that were equivalent to the linagliptin group. As evidence of evogliptin's powerful ability to control

ISSN: 0975-3583,0976-2833 VOL14, ISSUE 05, 2023

postprandial hyperglycemia, treatment with it led to considerably lower peak daily glucose levels, area under the curve for two hours after each meal (data not shown), and the percentage of time spent in hyperglycemia.

After a meal, a high glycaemic load may play a key role in causing oxidative stress, which directly damages the vascular endothelium. The onset and progression of diabetes problems are both possible [16]. This study found that evogliptin medication significantly reduced the levels of the oxidative stress indicators nitrotyrosine and TBARS, along with a reduction in glycaemic variability, which was mostly caused by postprandial glucose management. The presence of nitrotyrosine in diabetes patients' plasma is regarded as indirect proof of oxidative stress brought on by an imbalance in the synthesis of nitric oxide and peroxynitrite [17]. Plasma glucose levels and itrotyrosine concentrations showed a favourable correlation, but not HbA1c levels [18].

In numerous investigations [19,20], it has additionally been discovered that people with T2D had significantly higher serum levels of TBARS. Compared to diabetic patients without angiopathy, diabetic patients with angiopathy had considerably higher levels of TBARS, which may indicate increased lipid peroxidation [21]. When used in conjunction, evogliptin therapy can be a successful therapeutic approach for regulating postprandial glucose excursions and changes in glucose levels. Additionally, its benefits may have an impact on the reduction of vascular problems. Only the evogliptin group in this trial experienced significant drops in NAG levels at weeks 11 and 25, and there was no discernible difference between the other treatment groups. The lysosomal enzyme NAG, which is found in the proximal tubular cells, is excreted in the urine and appears to be a sensitive biomarker of early renal tubular injury. It has also been associated to glycaemic excursion in patients with T2D [22] for 25 weeks. These findings imply that evogliptin may preserve the kidneys by reducing the damage to the proximal renal tubule, which may be paired with the glucose-lowering impact of DPP-4 inhibition.

The safety evaluation findings revealed that the frequency of AEs was comparable between the two treatment groups over the course of the whole 25-week study period. Additionally, there was a very low incidence of SAEs throughout the entire study period. No significant ADRs were found. In fact, over the 25-week research period, there were no documented cases of symptomatic hypoglycemia in the evogliptin group. These findings confirm evogliptin's safety and tolerability.

CONCLUSION:

Treatment with evogliptin in individuals with T2D demonstrated robust glucose lowering efficacy and considerable improvement in glycaemic variability with outstanding safety and tolerability that were comparable to linagliptin treatment in the first 11-week original study and the 11-week extension phase.

CONFLICT OF INTEREST:

The authors state that they have no conflicts of interest.

FUNDING:

No outside funding was used for this study.

REFERENCES:

ISSN: 0975-3583,0976-2833 VOL14, ISSUE 05, 2023

1. American Diabetes Association. 6. Glycemic targets: standards of medical care in diabetes-2018. Diabetes Care. 2018;41:S55-S64.
2. Rama Chandran S, Tay WL, Lye WK, et al. Beyond HbA1c: comparing glycemic variability and glycemic indices in predicting hypoglycemia in type 1 and type 2 diabetes. Diabetes Technol Ther. 2018;20: 353-362.
3. Kovatchev BP. Metrics for glycaemic control - from HbA1c to continuous glucose monitoring. Nat Rev Endocrinol. 2017;13:425-436.
4. Cappon G, Vettoretti M, Sparacino G, Facchinetti A. Continuous glucose monitoring sensors for diabetes management: a review of technologies and applications. Diabetes Metab J. 2019;43:383-397.
5. Lu J, Ma X, Zhou J, et al. Association of time in range, as assessed by continuous glucose monitoring, with diabetic retinopathy in type 2 diabetes. Diabetes Care. 2018;41:2370-2376.
6. Cavalot F. Do data in the literature indicate that glycaemic variability is a clinical problem? Glycaemic variability and vascular complications of diabetes. Diabetes Obes Metab. 2013;15(Suppl 2):3-8.
7. Spallone V. Update on the impact, diagnosis and management of cardiovascular autonomic neuropathy in diabetes: what is defined, what is new, and what is unmet. Diabetes Metab J. 2019;43:3-30.
8. Monnier L, Mas E, Ginet C, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA. 2006;295:1681-1687.
9. Costantino S, Paneni F, Battista R, et al. Impact of glycemic variability on chromatin remodeling, oxidative stress, and endothelial dysfunction in patients with type 2 diabetes and with target HbA1c levels. Diabetes. 2017;66:2472-2482.
10. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of diabetes (EASD). Diabetes Care. 2018;41:2669-2701.
11. Kim MK, Ko SH, Kim BY, et al. 2019 clinical practice guidelines for type 2 diabetes mellitus in Korea. Diabetes Metab J. 2019;43: 398-406.
12. Goossen K, Graber S. Longer term safety of dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes mellitus: systematic review and meta-analysis. Diabetes Obes Metab. 2012;14:1061-1072.
13. Ahren B, Landin-Olsson M, Jansson PA, Svensson M, Holmes D, Schweizer A. Inhibition of dipeptidyl peptidase-4 reduces glycemia, sustains insulin levels, and reduces glucagon levels in type 2 diabetes. J Clin Endocrinol Metab. 2004;89:2078-2084.
14. Nabeno M, Akahoshi F, Kishida H, et al. A comparative study of the binding modes of recently launched dipeptidyl peptidase IV inhibitors in the active site. Biochem Biophys Res Commun. 2013;434:191-196.

ISSN: 0975-3583,0976-2833 VOL14, ISSUE 05, 2023

15. Gu N, Park MK, Kim TE, et al. Multiple-dose pharmacokinetics and pharmacodynamics of evogliptin (DA-1229), a novel dipeptidyl peptidase IV inhibitor, in healthy volunteers. Drug Des Devel Ther. 2014;8: 1709-1721.
16. Deacon CF, Lebovitz HE. Comparative review of dipeptidyl peptidase-4 inhibitors and sulphonylureas. Diabetes Obes Metab. 2016;18:333-347.
17. Kim MJ, Kim NY, Jung YA, et al. Evogliptin, a dipeptidyl peptidase-4 inhibitor, attenuates renal fibrosis caused by unilateral ureteral obstruction in mice. Diabetes Metab J. 2020;44:186-192.
18. Oh J, Kim AH, Lee S, et al. Effects of renal impairment on the pharmacokinetics and pharmacodynamics of a novel dipeptidyl peptidase-4 inhibitor, evogliptin (DA-1229). Diabetes Obes Metab. 2017;19: 294-298.
19. Eun Lee J, Kim JE, Lee MH, et al. DA-1229, a dipeptidyl peptidase IV inhibitor, protects against renal injury by preventing podocyte damage in an animal model of progressive renal injury. Lab Invest. 2016; 96:547-560.
20. Jung CH, Park CY, Ahn KJ, et al. A randomized, double-blind, placebo-controlled, phase II clinical trial to investigate the efficacy and safety of oral DA-1229 in patients with type 2 diabetes mellitus who have inadequate glycaemic control with diet and exercise. Diabetes Metab Res Rev. 2015;31:295-306.
21. Park J, Park SW, Yoon KH, et al. Efficacy and safety of evogliptin monotherapy in patients with type 2 diabetes and moderately elevated glycated haemoglobin levels after diet and exercise. Diabetes Obes Metab. 2017;19:1681-1687.
22. Hong SM, Park CY, Hwang DM, et al. Efficacy and safety of adding evogliptin versus sitagliptin for metformin-treated patients with type 2 diabetes: a 24-week randomized, controlled trial with open label extension. Diabetes Obes Metab. 2017;19:654-663.