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ORIGINAL RESEARCH

Comprehensive Evaluation of Combination Therapy with Basal Insulin and Either Lixisenatide or Vildagliptin in Japanese Patients with Type 2 Diabetes: A Randomized, Open-Label, Parallel-Group, Multicenter Study

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ABSTRACT

Introduction: We comprehensively evaluated the effects of combination therapy with insulin glargine and the incretin-based drugs lixisenatide or vildagliptin in Japanese patients with type 2 diabetes.

Methods: In this 12-week, randomized, open-label, parallel-group, multicenter study (GLP-ONE Kobe), the incretin-based drug sitagliptin was randomly switched to lixisenatide (20 μg/day, $n = 18$) or vildagliptin (100 mg/day, $n = 20$) in patients with inadequate glycemic control despite combination therapy with insulin glargine and sitagliptin. The dose of insulin glargine was titrated after the switch to maintain fasting blood glucose at approximately 110 mg/dL. The primary end points of

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the study were the change in glycosylated hemoglobin (HbA_{1c}) level between before and 12 weeks after the treatment switch, the proportion of patients achieving an HbA_{1c} level below 7.0%, and the postprandial increase in glucose concentration as assessed by self-monitoring of blood glucose.

Results: The change in HbA_{1c} level from baseline to 12 weeks did not differ significantly between the lixisenatide and vildagliptin groups ($-0.6 \pm 0.7\%$ and $-0.6 \pm 1.2\%$, respectively, $P = 0.920$). Neither the proportion of patients achieving an HbA_{1c} level below 7.0% nor the postprandial increase in glucose concentration was different between two groups. Body weight and serum low density lipoprotein (LDL) cholesterol level decreased significantly in the lixisenatide and vildagliptin groups, respectively. Both drugs were associated with mild gastrointestinal symptoms but not with severe hypoglycemia. Vildagliptin was associated with elevation of serum aspartate transaminase. Treatment satisfaction as assessed with the Diabetes Treatment Satisfaction Questionnaire did not differ significantly between the two groups.

Conclusion: The combinations of basal insulin and either lixisenatide or vildagliptin have similar efficacies with regard to improvement of glycemic control.

Trial Registration: This trial has been registered with UMIN (No. 000010769).

Keywords: Insulin glargine; Lixisenatide; Vildagliptin

INTRODUCTION

Reduction of both the postprandial glucose level and fasting plasma glucose (FPG) concentration is indispensable for the achievement and maintenance of effective glycemic control that prevents or ameliorates diabetic complications in individuals with type 2 diabetes [1, 2]. Administration of basal insulin reduces FPG through inhibition of hepatic glucose production [3–6], but it does not always result in a sufficient reduction in the postprandial glucose level. On the other hand, administration of bolus insulin before meals is effective for the control of postprandial hyperglycemia, although such treatment is associated with the risk of hypoglycemia and weight gain. Of the available alternatives to bolus insulin, incretin-related drugs including glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors appear to be a viable therapeutic option in combination with basal insulin and are less likely to be associated with the risk of hypoglycemia and weight gain [7–12].

Lixisenatide and liraglutide are the only once-daily GLP-1 receptor agonists available for use in combination with basal insulin under the current health insurance scheme in Japan. The short-acting agonist lixisenatide primarily lowers postprandial blood glucose levels through inhibition of gastric emptying, whereas the long-acting agonist liraglutide has a greater effect than lixisenatide on FPG, which is mediated predominantly via its insulinotropic and glucagonostatic actions [8]. Of the DPP-4 inhibitors currently available, vildagliptin was shown to be more effective in reducing hemoglobin A_{1c} (HbA_{1c}) levels than several other such drugs in a meta-analysis and systematic review [12]. Injectable lixisenatide and oral vildagliptin are thus each expected to be effective in combination with basal insulin for reducing not only postprandial hyperglycemia but also HbA_{1c} levels. However, to date, no study has directly compared the effects of lixisenatide and vildagliptin when these agents are administered in combination with basal insulin.

The aim of this study was to evaluate comprehensive effects of lixisenatide or vildagliptin used as an alternative to sitagliptin in Japanese individuals with type 2 diabetes and inadequate glycemic control despite combination therapy with sitagliptin and the basal insulin formulation insulin glargine.

METHODS

Study Subjects

This 12-week, randomized, open-label, parallel-group, multicenter study (GLP-ONE Kobe) was

performed with Japanese subjects with type 2 diabetes in accordance with the Declaration of Helsinki and its amendments, was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) as UMIN 000010769, and was approved by the Ethics Committee of Kobe University Hospital as well as by those of the nine additional participating institutions listed in at the end of the text. Written informed consent was obtained from all subjects prior to their randomization.

Patients were enrolled in the study if they met all of the following criteria: a diagnosis of type 2 diabetes, an age of 20–90 years, treatment with insulin glargine and sitagliptin (50 mg once daily) for at least 8 weeks, and an HbA_{1c} level of between 7.0% and 10.0%. They were enrolled irrespective of whether or not they had also received oral hypoglycemic agents (OHAs) other than sitagliptin. However, individuals were not enrolled if they had received either basal insulin other than insulin glargine or bolus insulin. Other exclusion criteria included hepatic dysfunction (serum transaminase levels of at least 2.5 times the upper limit of normal [ULN]); renal dysfunction (serum creatinine concentration of at least 1.3 mg/dL for men or at least 1.2 mg/dL for women); severe cardiac dysfunction; pregnancy or likelihood of becoming pregnant, or lactation; an acute metabolic abnormality; a psychiatric disorder that might impair sufficient understanding of the study objectives and processes; frequent hypoglycemia and consequent judgment by the attending physician of ineligibility for study participation; current treatment with oral steroids; and judgment by the attending physician of ineligibility for study entry for any other reason.

Study Protocol

All eligible patients were randomly assigned by a central allocation method based on a table of random numbers to either vildagliptin or lixisenatide as an alternative to sitagliptin (Fig. 1). The baseline data were collected after the randomization. Lixisenatide was initiated at 10 μg daily and was increased consecutively to 15 μg and then to 20 μg daily at 2-week intervals, with the 20-μg dose then being maintained until completion of the study. Vildagliptin was initiated and maintained at 100 mg/day (50 mg twice daily). The titration of insulin glargine was performed according to the attending physicians' instruction or the patients' own judgement to achieve a fasting blood glucose of approximately 110 mg/dL. In cases of fasting blood glucose level below 110 mg/dL, decreasing insulin glargine dose was also done by the attending physicians' decision or the patients' own judgement. Any concurrent OHA was discontinued or its dose adjusted at the discretion of the attending physician during patient visits at 4 and 8 weeks after study onset so as to ensure that FPG was maintained at or close to 110 mg/dL.

The primary end points of the study described in the protocol were change in HbA_{1c} level from baseline, the proportion of patients achieving an HbA_{1c} level below 7.0%, and the postprandial increase in glucose concentration as assessed by self-monitoring of blood glucose (SMBG), with the end point for sample size determination being the change in HbA_{1c} level in each group. The extent of the postprandial glucose increase was determined as the difference between 2-h postprandial (after breakfast, lunch, or dinner) and preprandial blood glucose values (ΔBG). ΔBG before the change in treatment was assessed on the basis of values measured during SMBG for at least 1 day and a maximum of 3 days between screening and switching, whereas ΔBG after the change in treatment was assessed on the basis of values measured during SMBG for at least 1 day and a maximum of 3 days between visits at 8 and 12 weeks. In the case of patients for whom SMBG data were available for more than 1 day, ΔBG was determined on the basis of mean glucose values. Change in ΔBG defined as $\Delta BG_{\text{after intervention}}$ minus $\Delta BG_{\text{before intervention}}$. Data from patients who had received a new OHA in addition to either investigational drug during the study or for whom the dose of any concurrent OHA was increased during the study were excluded from ΔBG analysis.

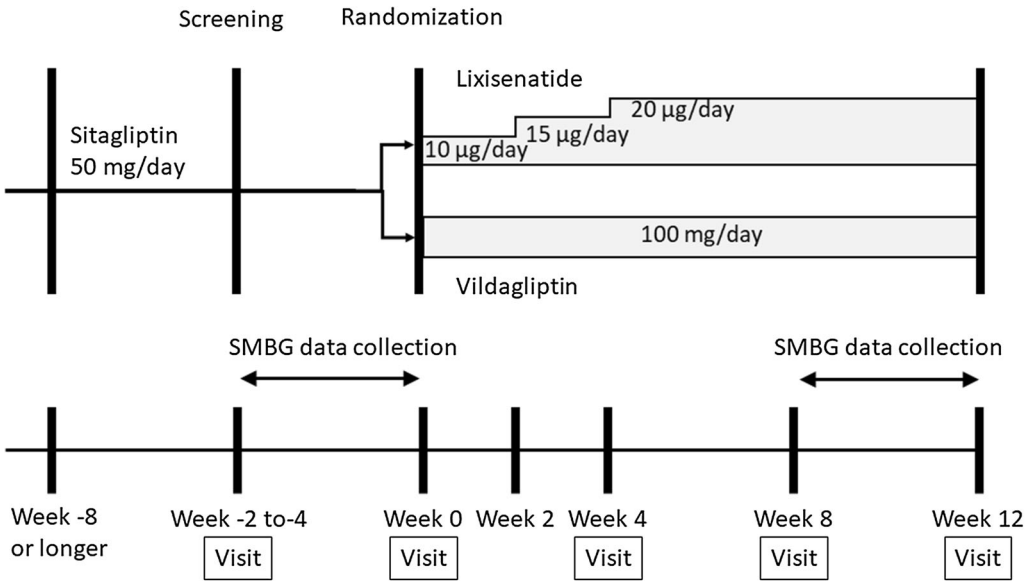

Fig. 1 Study protocol. SMBG self-monitoring of blood glucose

The secondary end points of the study included changes from baseline in fasting serum C-peptide immunoreactivity, body weight, blood pressure, and serum total cholesterol, low density lipoprotein (LDL)-cholesterol, and high density lipoprotein (HDL)-cholesterol levels as well as Diabetes Treatment Satisfaction Questionnaire (DTSQ) scores at 12 weeks. DTSQ scores are shown in Table S1. Serum triglyceride, HDL-cholesterol, and total cholesterol concentrations were measured by direct methods, whereas the serum LDL-cholesterol concentration was estimated with the Friedewald formula. DTSQ is a self-administered questionnaire for patients to assess their treatment satisfaction and perceived frequency of hyperglycemia and hypoglycemia. It consists of eight items each to be evaluated on a scale of 0–6, with overall treatment satisfaction determined on the basis of the total score for questionnaire items 1, 4, 5, 6, 7, and 8 [13]. All subjects were instructed to assess their quality of life with the use of the Japanese version of the DTSQ at 12 weeks. For safety evaluation, all patients were assessed for adverse events; vital signs; serum aspartate transaminase (AST), alanine transaminase (ALT), and creatinine levels; estimated glomerular filtration rate; and the urinary albumin excretion rate. Symptoms with respect to adverse events were collected at the patient visits. A severe hypoglycemic event was defined as an event requiring external assistance for recovery from hypoglycemia.

Statistical Analysis

Data are presented as mean ± SD for normally distributed data and as median (25–75% quartile) for data with non-normally distributions. A sample size of 34 patients per group was required to provide a power of 80% for detection of a statistically significant difference of 0.5 percentage points in HbA_{1c} level between baseline and 12 weeks after treatment onset, assuming an SD of 1.0% with an alpha value of 0.05. Considering potential patient dropout during the study, we determined the accrual goal to be 50 individuals for each group. Intergroup differences of normally or non-normally distributed data were tested for significance with the unpaired Student's *t* test or Mann–Whitney *U* test, respectively. Within-group comparisons of normally or non-normally distributed data were performed with the paired Student's *t* test and Wilcoxon signed-rank test, respectively. A *P* value of less than 0.05 was considered statistically significant. All

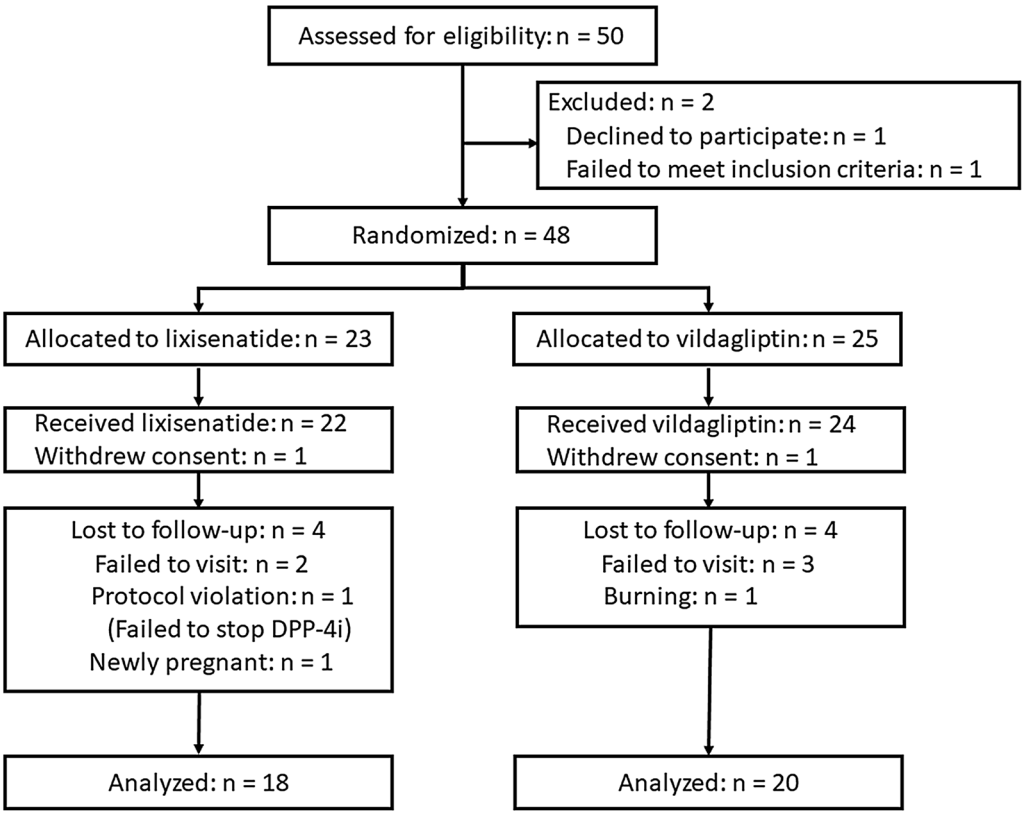

Fig. 2 Flow diagram of participant recruitment. DPP-4i dipeptidyl peptidase-4 inhibitor

statistical analysis was performed with SPSS ver. 22.0 software.

RESULTS

Study Subjects

A total of 48 patients were enrolled in the study and randomly assigned to the lixisenatide ($n = 23$) or vildagliptin ($n = 25$) treatment groups (Fig. 2). Of these patients, five individuals were subsequently excluded from each group. They withdrew consent after randomization ($n = 1$ in each group), failed to visit ($n = 2$ in the lixisenatide group and $n = 3$ in the vildagliptin group), violated the study protocol ($n = 1$ in the lixisenatide group), became pregnant ($n = 1$ in the lixisenatide group), had burning ($n = 1$ in the vildagliptin group). A total of 18 patients in the lixisenatide group (nine men and nine women, with a mean ± SD age of 61.3 ± 9.3 years) and 20 patients in the vildagliptin group (13 men and seven women, with a mean ± SD age of 64.7 ± 2.6 years) were thus available for analysis. In the lixisenatide group, the numbers of patients administered 10 μg, 15 μg, and 20 μg of the drugs were one, one, and sixteen, respectively.

Clinical Parameters

Characteristics of the study participants according to treatment group are presented in Table 1. None of the parameters differed significantly between the two groups at baseline. The change in HbA_{1c} level from baseline to 12 weeks after treatment onset did not differ significantly between the lixisenatide group and the vildagliptin group (Table 2). Four of the 18 patients (22.2%) in the lixisenatide group and 7 of the 20 patients (35.0%) in the vildagliptin group achieved the glycemic control goal of an HbA_{1c} level below 7.0% at 12 weeks, with these proportions not differing significantly. In the daily

Table 1 Principal clinical parameters for study participants at baseline

Parameter	Lixisenatide (n = 18)	Vildagliptin (n = 20)	Total (n = 38)	P
Male (n [%])	9 [50]	13 [65]	22 [58]	0.350
Disease duration (year)	15.1 ± 8.5	17.5 ± 9.5	16.3 ± 9.0	0.421
HbA_{1c} level (%)	7.9 (7.2–8.5)	7.8 (7.3–8.4)	7.8 (7.3–8.4)	0.725
FPG (mg/dL)	149.5 (122.5–173.0)	113.0 (82.5–187.0)	135.0 (99.8–171.3)	0.198
BMI (kg/m^2)	26.4 ± 3.7	24.6 ± 6.5	25.5 ± 5.4	0.310
BW (kg)	67.1 ± 11.2	64.3 ± 16.4	65.6 ± 14.1	0.542
SBP (mmHg)	134.9 ± 16.4	128.8 ± 17.7	131.7 ± 17.2	0.272
DBP (mmHg)	70.0 (64.0–78.5)	70.0 (64.0–79.5)	70.0 (64.0–78.5)	0.871
F-CPR (ng/mL)	1.9 ± 1.2	2.7 ± 1.7	2.3 ± 1.5	0.228
T-chol (mg/dL)	207.1 ± 35.2	201.5 ± 33.3	204.0 ± 33.6	0.679
LDL-C (mg/dL)	110.0 ± 25.5	115.5 ± 26.9	112.9 ± 26.0	0.522
HDL-C (mg/dL)	53.5 (42.0–63.0)	55.0 (45.0–68.8)	55.0 (44.5–63.5)	0.568
TG (mg/dL)	130.1 ± 59.5	118.7 ± 59.3	123.8 ± 58.5	0.626
Concomitant antidiabetic drug (n [%])				
None	5 [28]	4 [20]	9 [24]	
Sulfonylurea	8 [44]	12 [60]	20 [76]	
α-GI	6 [33]	9 [45]	15 [39]	
Metformin	4 [22]	4 [20]	8 [21]	
Thiazolidinedione	1 [6]	1 [5]	2 [5]	

Data are means ± SD, medians (25–75%), or n [%]. P values are for comparison between lixisenatide and vildagliptin groups

HbA_{1c} glycosylated hemoglobin, *FPG* fasting plasma glucose, *BMI* body mass index, *BW* body weight, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *F-CPR* fasting serum C-peptide immunoreactivity, *T-chol* total cholesterol, *LDL-C* low density lipoprotein-cholesterol, *HDL-C* high density lipoprotein-cholesterol, *TG* triglyceride, α-GI α-glucosidase inhibitor

blood glucose profile, change in blood glucose concentration at each time point did not differ between the lixisenatide and vildagliptin groups (Table 3). With regard to the extent of the postprandial increase in glucose level, change in ΔBG after the treatment switch did not differ significantly between the lixisenatide and vildagliptin groups at − 35.7 ± 56.7 mg/dL and − 14.2 ± 79.1 mg/dL after breakfast (P = 0.472), − 3.6 ± 61.6 mg/dL and 18.4 ± 62.7 mg/dL after lunch (P = 0.438), and − 9.9 ± 40.3 mg/dL and 8.7 ± 43.3 mg/dL after dinner (P = 0.360), respectively (Table 3). Both body weight (P = 0.036) and body mass index (P = 0.043) had decreased to a significantly greater extent at 12 weeks in the lixisenatide group than in the vildagliptin group (Table 2). The serum LDL-cholesterol concentration had decreased to a greater extent at 12 weeks in the vildagliptin group compared with the lixisenatide group (P = 0.044) (Table 2). There was no significant change in the dose of insulin glargine administered between before and after the change in treatment for either group [lixisenatide group, 14.5 (11.0–27.0) U at 12 weeks versus 13.5 (9.5–22.5) U at baseline (P = 0.140);

Table 2 Change in principal clinical parameters for study participants from baseline to 12 weeks after onset of treatment with lixisenatide or vildagliptin

Parameter	Lixisenatide	Vildagliptin	*P*
HbA_{1c} level (%)	− 0.6 ± 0.7	− 0.6 ± 1.2	0.920
FPG (mg/dL)	− 28.5 ± 40.1	− 29.9 ± 71.0	0.956
BMI (kg/m^2)	− 0.57 ± 0.66	− 0.02 ± 0.90	0.043*
BW (kg)	− 1.55 ± 1.79	− 0.08 ± 2.30	0.036*
SBP (mmHg)	− 3.0 (− 9.0 to 8.0)	1.0 (− 14.0 to 8.0)	0.812
DBP (mmHg)	1.5 (− 3.5 to 16.5)	0.0 (− 0.3 to 2.5)	0.481
F-CPR (ng/mL)	0.59 (− 1.20 to 1.68)	− 0.47 (− 2.45 to 0.46)	0.266
T-chol (mg/dL)	− 1.8 ± 23.0	− 13.0 ± 16.0	0.184
LDL-C (mg/dL)	2.9 ± 12.7	− 6.4 ± 14.5	0.044*
HDL-C (mg/dL)	− 2.0 (− 5.3 to 3.0)	− 3.0 (− 5.8 to 0.5)	0.291
TG (mg/dL)	− 16.8 ± 45.8	3.9 ± 78.0	0.461

Data are means ± SD or medians (25–75%). Abbreviations as in Table 1
*$P < 0.05$ for comparison between the lixisenatide and vildagliptin groups

Table 3 Change in daily blood glucose profile and postprandial glucose excursion assessed by self-monitoring of blood glucose for study participants from baseline to 12 weeks after onset of treatment with lixisenatide or vildagliptin

Daily blood glucose profile				Change in ΔBG at each meal			
	Lixisenatide	Vildagliptin	*P*		Lixisenatide	Vildagliptin	*P*
Before breakfast (mg/dL)	− 21.0 ± 26.0	− 18.2 ± 43.1	0.857	Breakfast	− 35.7 ± 56.7	− 14.2 ± 79.1	0.472
After breakfast (mg/dL)	− 56.7 ± 62.3	− 32.4 ± 75.8	0.421				
Before lunch (mg/dL)	− 6.5 (− 36.5 to 13.1)	− 25.3 (− 41.6 to 12.4)	0.762	Lunch	− 3.6 ± 61.6	18.4 ± 62.7	0.438
After lunch (mg/dL)	− 12.1 ± 61.1	15.9 ± 92.1	0.435				
Before dinner (mg/dL)	− 7.8 ± 58.1	− 0.3 ± 86.2	0.831	Dinner	− 9.9 ± 40.3	8.7 ± 43.3	0.360
After dinner (mg/dL)	− 17.6 ± 69.0	8.5 ± 77.6	0.462				
Bedtime (mg/dL)	− 16.7 ± 94.1	− 28.2 ± 51.5	0.778				

Data are means ± SD or medians (25–75%). *P* values are for comparison between lixisenatide and vildagliptin groups. ΔBG was defined for the extent of the postprandial glucose increase
BG blood glucose

Table 4 Diabetes Treatment Satisfaction Questionnaire (DTSQ) scores for study participants after 12 weeks of treatment with lixisenatide or vildagliptin

Item	Lixisenatide	Vildagliptin	*P*
Q1	5.0 (4.0–6.0)	5.0 (4.0–6.0)	0.492
Q2	3.8 ± 1.6	2.5 ± 1.8	0.039*
Q3	1.0 (0.0–3.0)	1.0 (0.0–2.5)	0.783
Q4	4.0 (4.0–6.0)	4.0 (3.0–5.0)	0.771
Q5	4.0 (3.5–5.0)	4.0 (3.0–5.5)	0.747
Q6	4.0 (3.0–5.0)	4.0 (4.0–5.5)	0.922
Q7	4.0 (3.0–5.0)	5.0 (3.0–6.0)	0.449
Q8	5.0 (4.0–6.0)	5.0 (3.5–6.0)	0.627
Treatment satisfaction	24.4 ± 6.8	26.6 ± 7.4	0.398

Data are means ± SD or medians (25–75%)
*$P < 0.05$ for comparison between lixisenatide and vildagliptin

Table 5 Clinical parameters for evaluation of treatment safety in study participants at baseline and after 12 weeks of treatment with lixisenatide or vildagliptin

Parameter	Lixisenatide			Vildagliptin		
	Baseline	12 weeks	*P*	Baseline	12 weeks	*P*
AST (IU/L)	23.0 (18.0–29.5)	26.0 (20.5–31.0)	0.775	21.5 (17.0–27.3)	24.0 (19.3–34.8)	0.033*
ALT (IU/L)	25.0 (18.0–34.5)	28.0 (20.0–34.0)	0.754	23.0 (13.5–27.0)	23.0 (17.0–28.5)	0.126
Cre (mg/dL)	0.74 (0.72–0.83)	0.72 (0.64–0.90)	0.286	0.80 (0.69–1.02)	0.78 (0.70–0.96)	0.777
eGFR (mL/min/1.73 m^2)	70.4 ± 14.2	73.3 ± 16.9	0.191	68.6 ± 19.4	68.7 ± 17.0	0.986
U-AER (mg/gCr)	18.8 (5.4–66.4)	14.3 (6.3–49.9)	0.446	16.8 (6.2–55.0)	8.7 (2.8–31.1)	0.123

Data are means ± SD or medians (25–75%)
*$P < 0.05$ for comparison between baseline and 12 weeks
AST aspartate transaminase, *ALT* alanine transaminase, *Cre* creatinine, *eGFR* estimated glomerular filtration rate, *U-AER* urinary albumin excretion rate

vildagliptin group, 10.0 (5.3–17.0) U at 12 weeks versus 10.0 (5.3–15.5) U at baseline ($P = 0.825$)]. There were no significant differences in the administered insulin doses at 12 weeks ($P = 0.051$).

DTSQ

Overall DTSQ scores for treatment satisfaction were not significantly different between the two groups at 12 weeks ($P = 0.398$) (Table 4). However, analysis of DTSQ scores by questionnaire item revealed that the score for Q2 (perceived frequency of hyperglycemia) was significantly lower in the vildagliptin group compared with the lixisenatide group ($P = 0.039$). No correlation was apparent between DTSQ scores at 12 weeks and the changes in HbA_{1c} level or body weight (data not shown).

Adverse Events

Constipation was reported in one patient in the vildagliptin group, whereas vomiting, nausea,

and fullness were reported in one, one, and two patients, respectively, in the lixisenatide group. All reported adverse events were mild. The frequency of hypoglycemia as determined on the basis of symptoms or a blood glucose level below 70 mg/dL did not differ significantly between the two groups, with no severe hypoglycemic events being reported in either group.

Other Clinical Parameters

Of the additional biochemical parameters evaluated, serum AST was significantly elevated ($P = 0.033$) at 12 weeks compared with baseline in the vildagliptin group (Table 5), with the final value being more than 2.5 times the ULN in one patient (85 IU/L at 12 weeks versus 28 IU/L at baseline). Neither serum ALT or creatinine levels, estimated glomerular filtration rate, nor urinary albumin excretion rate differed significantly between before and after the change in treatment in either group (Table 5).

Concurrent Medications

The study treatment led to dose reductions or discontinuation of other OHAs in two patients (sulfonylurea discontinued in both) in the lixisenatide group and two patients (metformin or sulfonylurea discontinued in one each) in the vildagliptin group, no dose change in 15 patients in the lixisenatide group and 16 patients in the vildagliptin group, and an increase in dose for two patients (α-glucosidase inhibitor in both) in the lixisenatide group and one patient (sulfonylurea) in the vildagliptin group. The study treatment led to no change in the administration of antihypertensive or antidyslipidemic agents in either group.

DISCUSSION

The present study is the first randomized trial to comprehensively evaluate the effects of lixisenatide and vildagliptin, each as an alternative to sitagliptin, in individuals with type 2 diabetes who were not able to achieve adequate glycemic control during combination therapy with insulin glargine and sitagliptin. Our results reveal that the efficacy with regard to improvement of glycemic control was similar for both treatments. However, whereas treatment with lixisenatide reduced body weight, that with vildagliptin reduced the serum LDL-cholesterol concentration. Given that in addition lixisenatide is administered by injection and expensive compared with vildagliptin, the background of patients including their financial situation, the absence or presence of obesity, and the lipid profile should be taken into consideration in therapy selection.

Previous studies demonstrated that GLP-1 analogues were more potent in lowering HbA_{1c} levels than DPP-4 inhibitors [14, 15]. However, there was no difference in the improvement of HbA_{1c} between lixisenatide and vildagliptin in our study. The reason may be the short period of the intervention in the present study. HbA_{1c}-lowering effects of DPP-4 inhibitors were generally reduced 3–6 months after administration among 20–39% of patients [16]. Thus, the present study may have finished before the effects of DPP-4 inhibitors were reduced. In addition, postprandial glucose excursion is associated with the risk for chronic diabetic complications [17], indicating that appropriate control of the postprandial glucose level is important for the prevention of such complications. Incretin-based drugs have been found to differ in efficacy with regard to limiting the postprandial increase in glucose concentration. Lixisenatide was thus shown to reduce postprandial glucose to a significantly greater extent compared with sitagliptin [18, 19]. Vildagliptin also reduced both the mean amplitude of glycemic excursions and postprandial glucose to a significantly greater extent than sitagliptin [20]. We have now shown that there was no significant difference in the postprandial change in glucose concentration between lixisenatide and vildagliptin in patients also receiving basal insulin. However, it should be noted that patients were evaluated for postprandial glucose over a short period of 1–3 days in our study. A continuous glucose monitoring-based, long-term, and detailed study is therefore required to accurately evaluate the efficacies of lixisenatide and

vildagliptin with regard to limitation of postprandial glucose excursion.

Our results also show that combination treatment with lixisenatide led to a significant decrease in body weight compared with vildagliptin. It has been generally assumed that treatment with DPP-4 inhibitors does not affect body weight, whereas that with GLP-1 receptor agonists leads to a reduction in body weight [7–9, 21]. Indeed, the GetGoal-L and GetGoal-L-Asia trials found that lixisenatide treatment resulted in a greater reduction in body weight compared with placebo in patients also receiving insulin glargine [10, 22]. With regard to lipid profile, combination treatment with vildagliptin reduced the serum LDL-cholesterol level significantly compared with lixisenatide, consistent with previous results showing that vildagliptin lowers serum LDL-cholesterol [23, 24]. The treatment of type 2 diabetes with GLP-1 receptor agonists is often associated with the reduction in the LDL-C levels [25]. We do not know the reason why the LDL-C levels were increased by the treatment with lixisenatide in this study. It is possible that the effects of GLP-1 receptor agonist on LDL-C may differ in each formulation. It is also possible that the effects may be influenced by concomitant medications. To our knowledge, no head-to-head comparisons of GLP-1 receptor agonists and DPP-4 inhibitors have previously been undertaken with regard to their effects on body weight and lipid profile when administered in combination with basal insulin.

We found that there was no significant difference in overall treatment satisfaction score at 12 weeks between the lixisenatide and vildagliptin groups. A previous study found no decrease in quality of life for Japanese patients switched from sitagliptin to the once-daily injectable drug liraglutide or to vildagliptin [14]. On the other hand, we found that the Q2 score (perceived frequency of hyperglycemia) was significantly lower in the vildagliptin group than in the lixisenatide group. Given that there was no significant difference in glycemic parameters (FPG and HbA_{1c} level) at 12 weeks between the lixisenatide and vildagliptin groups, the reason for this difference in Q2 is unclear, although twice-daily drug administration might alleviate a sense of anxiety with regard to hyperglycemia. In addition, the increased frequency of injections associated with lixisenatide administration even among patients already receiving insulin injections might contribute to the lack of a difference in overall treatment satisfaction between the two groups in spite of the significant reduction in body weight in the lixisenatide group.

Both lixisenatide and vildagliptin were associated with mild gastrointestinal symptoms but no severe adverse events in the present study. Given that incretin-based drugs rely on glucose-dependent stimulation of insulin secretion and inhibition of glucagon secretion, they are less likely to be associated with the risk of hypoglycemia. Indeed, neither lixisenatide nor vildagliptin treatment resulted in severe episodes of hypoglycemia, even when combined with basal insulin, in our study. We found that treatment with vildagliptin was associated with mildly elevated AST levels. Previous systematic review and meta-analysis of vildagliptin efficacy and safety reported no increase in hepatic enzymes with this drug [26, 27], although vildagliptin is contraindicated for patients with severe liver dysfunction in Japan. The mechanism underlying vildagliptin-induced liver dysfunction is unclear, although it may be related to the observation that vildagliptin and its metabolite M20.7 induced expression of the pro-inflammatory proteins S100A8 and S100A9 in mouse liver and immune cell lines [28]. Careful attention is thus warranted when vildagliptin is administered in patients with liver dysfunction.

Our study has several limitations. First, the sample size is relatively small. Second, it included only Japanese patients with relatively well-controlled diabetes. It therefore remains unclear whether the study results may be readily generalizable to populations that differ in body composition or ethnicity. Third, it did not achieve the projected accrual goal. Fourth, whereas the dose of insulin glargine was titrated so as to achieve an FPG of approximately 110 mg/dL, no consistent elaborate algorithm for dose titration was adopted. The median FPG values at completion of the study were thus 123.5 and 113.0 mg/dL in the lixisenatide and

vildagliptin groups, respectively, with the proportion of patients achieving the glycemic goal in these groups being 50.0% and 41.7%, respectively.

CONCLUSIONS

Combination therapy with insulin glargine and either lixisenatide or vildagliptin led to similar improvements in glycemic control in patients with type 2 diabetes. Further studies are required to determine whether these findings are generalizable to patients with different backgrounds.

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Compliance with Ethics Guidelines. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract. 1995;28(2):103–17.

2. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33. Lancet. 1998;352(9131):837–53.

3. Bretzel RG, Nuber U, Landgraf W, Owens DR, Bradley C, Linn T. Once-daily basal insulin glargine versus thrice-daily prandial insulin lispro in people with type 2 diabetes on oral hypoglycaemic agents (APOLLO): an open randomised controlled trial. Lancet. 2008;371(9618):1073–84.

4. Holman RR, Farmer AJ, Davies MJ, 4-T Study Group, et al. Three-year efficacy of complex insulin regimens in type 2 diabetes. N Engl J Med. 2009;361(18):1736–47.

5. Aschner P, Chan J, Owens DR, et al. EASIE Investigators. Insulin glargine versus sitagliptin in insulin-naive patients with type 2 diabetes mellitus uncontrolled on metformin (EASIE): a multicentre, randomised open-label trial. Lancet. 2012;379(9833):2262–9.

6. Rojas JM, Schwartz MW. Control of hepatic glucose metabolism by islet and brain. Diabetes Obes Metab. 2014;16(suppl 1):33–40.

7. Nauck MA. Incretin-based therapies for type 2 diabetes mellitus: properties, functions, and clinical implications. Am J Med. 2011;124(1 suppl):S3–18.

8. Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. Nat Rev Endocrinol. 2012;8(12):728–42.

9. Secher A, Jelsing J, Baquero AF, et al. The arcuate nucleus mediates GLP-1 receptor agonist liraglutide-dependent weight loss. J Clin Invest. 2014;124(10):4473–88.

10. Seino Y, Min KW, Niemoeller E, Takami A, EFC10887 GETGOAL-L Asia Study Investigators. Randomized, double-blind, placebo-controlled trial of the once-daily GLP-1 receptor agonist lixisenatide in Asian patients with type 2 diabetes insufficiently controlled on basal insulin with or without a sulfonylurea (GetGoal-L-Asia). Diabetes Obes Metab. 2012;14(10):910–7.

11. Mathieu C, Rodbard HW, Cariou B, et al. A comparison of adding liraglutide versus a single daily dose of insulin aspart to insulin degludec in subjects with type 2 diabetes (BEGIN: VICTOZA ADD-ON). Diabetes Obes Metab. 2014;16(7):636–44.

12. Aroda VR, Henry RR, Han J, et al. Efficacy of GLP-1 receptor agonists and DPP-4 inhibitors: meta-analysis and systematic review. Clin Ther. 2012;34(6):1247–58.

13. Bradley C. The diabetes treatment satisfaction questionnaire: DTSQ. In: Bradley C, editor. Handbook of psychology and diabetes: a guide to psychological measurement in diabetes research and practice. Chur: Harwood; 1994. p. 111–32.

14. Takeshita Y, Takamura T, Kita Y, Establishment of Rationale for Antiaging Diabetic Medicine (ERA-DM) Study Chapter 2 Group, et al. Vildagliptin vs liraglutide as a second-line therapy switched from sitagliptin-based regimens in patients with type 2 diabetes: a randomized, parallel-group study. J Diabetes Invest. 2015;6(2):192–200.

15. de Wit HM, Te Groen M, Rovers MM, Tack CJ. The placebo response of injectable GLP-1 receptor agonists vs. oral DPP-4 inhibitors and SGLT-2 inhibitors: a systematic review and meta-analysis. Br J Clin Pharmacol. 2016;82(1):301–14.

16. Kubota A, Yabe D, Kanamori A, et al. Factors influencing the durability of the glucose-lowering

effect of sitagliptin combined with a sulfonylurea. J Diabetes Investig. 2014;5(4):445–8.

17. Ceriello A. The post-prandial state and cardiovascular disease: relevance to diabetes mellitus. Diabetes Metab Res Rev. 2000;16(2):125–32.

18. Yamada Y, Senda M, Naito Y, et al. Reduction of postprandial glucose by lixisenatide vs sitagliptin treatment in Japanese patients with type 2 diabetes on background insulin glargine: a randomized phase IV study (NEXTAGE Study). Diabetes Obes Metab. 2017;19(9):1252–9.

19. Van Gaal L, Souhami E, Zhou T, Aronson R. Efficacy and safety of the glucagon-like peptide-1 receptor agonist lixisenatide versus the dipeptidyl peptidase-4 inhibitor sitagliptin in young (< 50 years) obese patients with type 2 diabetes mellitus. J Clin Transl Endocrinol. 2014;1(2):31–7.

20. Sakamoto M, Nishimura R, Irako T, Tsujino D, Ando K, Utsunomiya K. Comparison of vildagliptin twice daily vs. sitagliptin once daily using continuous glucose monitoring (CGM): crossover pilot study (J-VICTORIA study). Cardiovasc Diabetol. 2012;11:92. https://doi.org/10.1186/1475-2840-11-92.

21. Nauck M. Incretin therapies: highlighting common features and differences in the modes of action of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. Diabetes Obes Metab. 2016;18(3):203–16.

22. Riddle MC, Aronson R, Home P, et al. Adding once-daily lixisenatide for type 2 diabetes inadequately controlled by established basal insulin: a 24-week, randomized, placebo-controlled comparison (GetGoal-L). Diabetes Care. 2013;36(9):2489–96.

23. Evans M, Schweizer A, Foley JE. Blood pressure and fasting lipid changes after 24 weeks' treatment with vildagliptin: a pooled analysis in > 2000 previously drug-naïve patients with type 2 diabetes mellitus. Vasc Health Risk Manag. 2016;12:337–40.

24. Strózik A, Stęposz A, Basiak M, Drożdż M, Okopień B. Multifactorial effects of vildagliptin added to ongoing metformin therapy in patients with type 2 diabetes mellitus. Pharmacol Rep. 2015;67(1):24–31.

25. Sun F, Wu S, Wang J, et al. Effect of glucagon-like peptide-1 receptor agonists on lipid profiles among type 2 diabetes: a systemic review and network meta-analysis. Clin Ther. 2015;37(1):225–41.

26. Bekiari E, Rizava C, Athanasiadou E, et al. Systematic review and meta-analysis of vildagliptin for treatment of type 2 diabetes. Endocrine. 2016;52(3):458–80.

27. Ligueros-Saylan M, Foley JE, Schweizer A, Couturier A, Kothny W. An assessment of adverse effects of vildagliptin versus comparators on the liver, the pancreas, the immune system, the skin and in patients with impaired renal function from a large pooled database of phase II and III clinical trials. Diabetes Obes Metab. 2010;12(6):495–509.

28. Asakura M, Karaki F, Fujii H, Atsuda K, Itoh T, Fujiwara R. Vildagliptin and its metabolite M20.7 induce the expression of S100A8 and S100A9 in human hepatoma HepG2 and leukemia HL-60 cells. Sci Rep. 2016;6:35633.