Low body mass index and old age are useful in predicting the hemoglobin A1c-lowering effect of switching from sitagliptin to dulaglutide in Japanese patients with type 2 diabetes mellitus: a single-center, open-label, single-arm, pilot study

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Abstract

Aims The purpose of this study was to clarify the predictive clinical characteristics of therapy switching from sitagliptin to dulaglutide in patients with type 2 diabetes mellitus.

Methods This single-center, open-label, investigator-initiated pilot study was conducted in 40 patients with type 2 diabetes mellitus. The patients, who had been treated with 50 mg sitagliptin daily for at least 6 months were switched to 0.75 mg dulaglutide weekly.

Results A total of 36 patients could be followed for 24 weeks of treatment with dulaglutide. They were assessed for several clinical parameters before the start of and 24 weeks after the study. Multiple linear regression analysis was used to search for independent predictors of reduction of hemoglobin A1c (HbA1c) levels after 24 weeks of treatment switching from sitagliptin to dulaglutide. Dulaglutide administration for 24 weeks resulted in significant reductions in fasting plasma glucose (FPG), HbA1c, and low-density lipoprotein cholesterol (LDL-C) levels. In addition, baseline HbA1c, FPG, body mass index (BMI), and age were significantly correlated with the change in HbA1c levels (Δ HbA1c). Furthermore, multiple linear regression analysis revealed that BMI and age significantly correlated with Δ HbA1c.

Conclusion In summary, our prospective 24-week study showed that baseline low BMI and old age are significantly useful in predicting the HbA1c-lowering effect of switching from sitagliptin to dulaglutide.

Trial Registration UMIN Clinical Trials Registry (UMIN000023245).

Keywords Type 2 diabetes mellitus · Dulaglutide · Sitagliptin · Glucagon-like peptide-1 receptor agonist · Predictive clinical characteristics

Introduction

There is a continuing unmet need for novel glucose-lowering therapies that provide durable glycemic control while avoiding hypoglycemia, weight gain, and fluid retention, which are recognized problems associated with a number

of existing glucose-lowering drugs [1–3]. The Japan Diabetes Society (JDS) recommends a careful approach to the treat older patients with diabetes mellitus to avoid adverse events, such as hypoglycemia due to sulfonylureas (SU), lactic acidosis (due to biguanides), and edema and heart failure (due to thiazolidinediones) [4]. Dulaglutide is a long-acting human glucagon-like peptide-1 (GLP-1) receptor agonist approved as a weekly subcutaneous injection for the treatment of type 2 diabetes mellitus. It is administered with a single use pen with no requirement for reconstitution or dialing of a dose [5]. It is not renally excreted and pharmacokinetic studies have shown that neither age nor renal function affects its actions, thereby eliminating the need for dose adjustment. Incretin-based therapies, including dipeptidyl peptidase-4 (DPP-4) inhibitors and GLP-1 receptor

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agonists, stimulate insulin secretion in a glucose-dependent manner resulting in lower risk of hypoglycemia when used as monotherapy or in combination with agents that do not increase insulin levels [6]; therefore, they could be a good alternative for the elderly.

Although fewer gastrointestinal adverse events are associated with sitagliptin than those with dulaglutide, clinical trials have shown that dulaglutide is superior to sitagliptin with respect to glycemic control and body weight reduction when tested head-to-head [7]. However, limited clinical evidence exists to guide treatment strategy when initial second-line treatment with sitagliptin fails to provide adequate glycemic control.

To use switching from sitagliptin to dulaglutide as a therapy option for patients with type 2 diabetes mellitus, it is important to know the predictive clinical characteristics for its therapeutic efficacy. Therefore, we performed regression analyses to search for independent predictors of the reduction in HbA1c level after 24 weeks of dulaglutide treatment in Japanese patients with type 2 diabetes mellitus.

Materials and methods

Subjects

This single-center, open-label, investigator-initiated pilot study was conducted in 40 patients with type 2 diabetes mellitus whose HbA1c levels were higher than 6.0%. Patients were enrolled between July and September 2016. The specific patient eligibility criteria for inclusion were as follows: male and female patients with type 2 diabetes mellitus; age ≥ 20 years; and treatment with hypoglycemic agents unchanged for at least 6 months. Patients were excluded if they had type 1 diabetes; had nephropathy (serum creatinine: > 1.1 mg/dL); were pregnant or breastfeeding; intended to conceive; were female of childbearing age who were not using adequate contraceptive methods; had known/suspected allergy to trial medication(s), excipients, or related products; or had any contraindications to dulaglutide therapy.

Forty patients with type 2 diabetes mellitus who had been treated with 50 mg sitagliptin daily for at least 6 months were switched to 0.75 mg dulaglutide weekly. Several clinical parameters were assessed including body mass index (BMI); systolic blood pressure (SBP); diastolic blood pressure (DBP); and fasting plasma glucose (FPG), HbA1c, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ -glutamyltransferase (GGT), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), creatinine, and uric acid levels before the start of and 24 weeks after the study. The primary outcome of

this study was a change in HbA1c levels at 24 weeks after the start of the study (Δ HbA1c).

Safety assessments included adverse events, hypoglycemia, vital signs (pulse rate and blood pressure), and laboratory variables. Hypoglycemia was defined as a plasma glucose concentration of ≤ 70 mg/dL and/or symptoms and/or signs attributable to hypoglycemia. Severe hypoglycemia was defined as an episode requiring the assistance of another person to actively administer therapy [8].

The study protocol conformed to the principles of the Declaration of Helsinki, and the study was approved by an institutional review committee at Iwasaki Naika Clinic (date of approval 5 July 2016; approval no. 00004). Written informed consent was obtained from all the patients. This study is registered at the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN000023245).

Statistical analysis

Data are expressed as mean $\pm$ standard deviation, unless indicated otherwise. Differences between two variables were examined for statistical significance using two-tailed Student's paired *t* test where appropriate. The changes of in HbA1c, FPG, and LDL-C levels from baseline to 24 weeks after switching from sitagliptin to dulaglutide are represented as Δ HbA1c, Δ FPG and Δ LDL-C, respectively. Because the relationships between continuous variables (*i.e.*, age, duration of diabetes, BMI, SBP, DBP, FPG, HbA1c, AST, ALT, GGT, LDL-C, HDL-C, TG, creatinine, uric acid and Δ HbA1c) were nonlinear, correlations between sets of two independent continuous variables were determined using Spearman's rank correlation coefficient. Multiple regression analysis was used to determine independent predictors of Δ HbA1c, Δ FPG and Δ LDL-C. Independent variables were selected the variables which were significantly correlated with Δ HbA1c in univariate analysis (*i.e.*, age, BMI, HbA1c, and FPG). HbA1c was excluded from this analysis because HbA1c and FPG were significantly covariate variables ($r = 0.665$, $p < 0.0001$). Therefore, the independent variables are age, BMI and FPG. We performed multiple regression analysis Δ FPG and Δ LDL-C, as same as Δ HbA1c. Comparisons between the 4 subgroups were performed with an analysis of one factor ANOVA. The level of statistical significance was set at $p < 0.05$. All statistical analyses were performed with StatView version 5.0 for Windows (SAS Institute Inc., Cary, NC).

Results

Patient baseline characteristics

In total, 40 patients were enrolled in the present study, and 36 patients were successfully followed for 24 weeks of

Fig. 1 Patient attrition

Table 1 Safety assessments up to week 24

	All patients (n = 40)
Deaths	0
Serious adverse event	0
Nasopharyngitis	0
Nausea	3
Diarrhea	0
Constipation	0
Vomiting	0
Hypoglycemia	1
Severe hypoglycemia	0

treatment with dulaglutide. Four patients were excluded from analysis: three had nausea and the one dropped out (Fig. 1). Hypoglycemia was seen in one patient receiving a sulfonylurea drug (Table 1). The baseline clinical characteristics of the study subjects are shown in Table 1. Mean age was 66.7 ± 11.1 years, mean HbA1c level was $7.80 \pm 0.99\%$, mean BMI was 28.7 ± 5.3 kg/m², and mean disease duration was 17.9 ± 9.1 years. Table 1 also shows the number of participants who received antidiabetic agent(s) prior to the study.

Clinical characteristics of 36 patients at baseline and after 24 weeks of treatment with dulaglutide

Switching from sitagliptin to dulaglutide for 24 weeks resulted in significant reductions in FPG (137.5 ± 15.8 – 123.9 ± 15.2 mg/dL, $p < 0.0001$), HbA1c

(7.80 ± 0.99 – $7.25 \pm 0.71\%$, $p < 0.0001$), and LDL-C (90.5 ± 20.5 – 78.6 ± 18.0 mg/dL, $p = 0.0010$) levels (Table 2).

Correlation between baseline characteristics and change in HbA1c, FPG, and LDL-C levels

We examined the correlation between the baseline characteristics and the change in HbA1c levels (Δ HbA1c) and found that baseline HbA1c levels ($r = -0.704$, $p < 0.0001$), FPG levels ($r = -0.484$, $p = 0.0028$), BMI ($r = 0.377$, $p = 0.0251$) and age ($r = -0.600$, $p < 0.0001$) were significantly correlated with Δ HbA1c (Table 3). The distribution plots of Δ HbA1c vs. baseline HbA1c levels, FPG levels, BMI, and age are shown in Fig. 2. In addition, we also examined the correlation between baseline characteristics and changes in FPG levels (Δ FPG) and LDL-C levels (Δ LDL-C). We found that baseline FPG levels significantly correlated with Δ FPG ($r = -0.582$, $p = 0.0002$). The distribution plot of Δ FPG vs. baseline FPG levels are shown in Fig. 2. We also found that baseline LDL-C levels significantly correlated with Δ LDL-C ($r = -0.596$, $p = 0.0001$). The distribution plot of Δ LDL-C vs. baseline LDL-C levels is shown in Fig. 2.

Multivariate linear regression analysis of baseline characteristics to assess the contribution to change in HbA1c, FPG, and LDL-C levels

To assess the contribution to change in HbA1c levels, we performed multivariate linear regression analysis utilizing baseline clinical characteristics. We found that baseline BMI and age significantly correlated with Δ HbA1c, suggesting that these characteristics may be predictive factors for the efficacy of switching from sitagliptin to dulaglutide (Table 4). We performed a similar analysis to assess the contribution to change in FPG levels and LDL-C levels. We found that baseline FPG levels significantly correlated with Δ FPG and baseline LDL-C levels significantly correlated with Δ LDL-C (Tables 5, 6).

Discussion

Herein, we investigated the efficacy of treatment switching from sitagliptin to dulaglutide in 40 Japanese outpatients with type 2 diabetes mellitus; 36 patients were successfully followed for a 24-week treatment period. We demonstrated that dulaglutide administration for 24 weeks resulted in significant reductions in FPG, HbA1c, and LDL-C levels in clinical practice (Table 2). Miyagawa et al. reported that in Japanese patients with type 2 diabetes, weekly dulaglutide (0.75 mg) was superior to placebo and non-inferior to

Table 2 Clinical characteristics of 36 patients at baseline and after 24 weeks of treatment with dulaglutide

Variables	Before treatment	After 24 weeks	<i>p</i> value
<i>N</i>	36		
Sex (male/female)	15/21		
Age (years)	66.7 ± 11.1		
Duration of diabetes (years)	17.9 ± 9.1		
BMI (kg/m ²)	28.7 ± 5.3	28.4 ± 5.3	0.0807
SBP (mmHg)	128.1 ± 11.7	126.5 ± 14.2	0.4410
DBP (mmHg)	71.5 ± 12.3	71.2 ± 11.2	0.8381
FPG (mg/dL)	137.5 ± 15.8	123.9 ± 15.2	< 0.0001
HbA1c (%)	7.80 ± 0.99	7.25 ± 0.71	< 0.0001
AST (IU/L)	25.1 ± 14.3	25.4 ± 18.0	0.8103
ALT (IU/L)	27.2 ± 14.0	29.1 ± 19.3	0.2952
GGT (IU/L)	46.0 ± 30.3	45.2 ± 32.3	0.7230
LDL-C (mg/dL)	90.5 ± 20.4	78.6 ± 18.0	0.0010
HDL-C (mg/dL)	46.9 ± 19.4	67.2 ± 18.5	0.1303
TG (mg/dL)	133.3 ± 52.3	131.5 ± 44.5	0.7734
Creatinine (mg/dL)	0.69 ± 0.22	0.71 ± 0.17	0.2374
Uric acid (mg/dL)	4.93 ± 1.35	4.66 ± 1.10	0.0818
Antidiabetic medications (<i>n</i>)			
Sulfonylurea	22		
Metformin	14		
Thiazolidinedione	5		
DPP-4 inhibitor	36		
SGLT2 inhibitor	17		
Insulin injection	19		
Hypolipidemic agents (<i>n</i>)			
Statins	26		
Fibrates	4		
Antihypertensive agents (<i>n</i>)			
ARBs/ACEIs	26		
CCBs	18		
β-blockers	3		
Diuretics	12		

Data are mean ± SD

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FPG* fasting plasma glucose, *HbA1c* hemoglobin A1c, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *GGT* γ-glutamyltransferase, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *TG* triglycerides, *DPP-4* dipeptidyl peptidase-4, *SGLT2* sodium-glucose co-transporter-2, *ARBs* angiotensin II receptor blockers, *ACEIs* angiotensin-converting enzyme inhibitors, *CCBs* calcium channel blockers

daily liraglutide (0.9 mg) for reduction in HbA1c levels at 26 weeks [9]. Araki et al. reported that dulaglutide as an add-on to a sulfonylurea and/or metformin significantly improved glycemic control in Japanese type 2 diabetes patients in a randomized phase 3 study [10]. Emoto et al. reported that the mean changes in HbA1c levels from baseline were − 1.93% in dulaglutide + sulfonylureas subgroup;

Table 3 Correlation of ΔHbA1c with other associated baseline variables

	ΔHbA1c	
	<i>r</i> value	<i>p</i> value
Age	− 0.600	< 0.0001
Duration of diabetes	− 0.158	0.3669
BMI	0.377	0.0251
SBP	0.001	0.9959
DBP	0.127	0.4715
FPG	− 0.484	0.0028
HbA1c	− 0.704	< 0.0001
AST	0.078	0.6592
ALT	0.248	0.1521
GGT	0.189	0.2802
LDL-C	− 0.156	0.3727
HDL-C	− 0.055	0.7536
TG	− 0.086	0.6271
Creatinine	0.207	0.2342
Uric acid	− 0.198	0.2558

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FPG* fasting plasma glucose, *HbA1c* hemoglobin A1c, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *GGT* γ-glutamyltransferase, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *TG* triglycerides

− 1.58% in dulaglutide + biguanides subgroup and − 1.71% in dulaglutide + thiazolidinedione subgroup in phase 3 studies of dulaglutide in Japanese diabetes mellitus patients [11]. However, the mean changes in HbA1c levels from baseline were − 0.54% in sulfonylureas subgroup (*n* = 22); − 0.32% in biguanides subgroup (*n* = 14) and − 0.10% in thiazolidinedione subgroup (*n* = 5) in this study. Previously reported results for comparisons between dulaglutide and sitagliptin after 52 weeks, the primary endpoint in AWARD-5, and placebo after 26 weeks showed that dulaglutide provided improved glycemic control compared with sitagliptin and placebo [12]. In this study, patients with type 2 diabetes mellitus were switched from sitagliptin to dulaglutide weekly and experienced further clinically relevant reductions in FPG, HbA1c, and LDL-C levels.

In addition, age, BMI, FPG levels, and HbA1c levels significantly correlated with ΔHbA1c (Table 3). Multiple linear regression analysis also revealed that baseline age and BMI significantly correlated with ΔHbA1c. Therefore, we demonstrated that baseline age and BMI contributed to the HbA1c-lowering effect of switching from sitagliptin to dulaglutide in Japanese patients with type 2 diabetes mellitus (Table 4).

Dulaglutide has varied effects on plasma lipids. Wysham et al. reported that LDL-C levels were significantly decreased after 26 weeks of treatment with dulaglutide and HDL-C levels were unchanged. [13]. It was reported

Fig. 2 Distribution plots of ΔHbA1c (%) **a** versus baseline HbA1c (%), **b** baseline FPG (mg/dL), **c** baseline BMI, and **d** age (years). **e** Distribution plots of ΔFPG (mg/dL) versus baseline FPG (mg/dL). **f** Distribution plot of $\Delta\text{LDL-C}$ (mg/dL) versus baseline LDL-C (mg/dL)

Table 4 Multiple regression analysis of the relationship between ΔHbA1c and other associated variables

Risk factors	Regression coefficient	Standard error	Standardized regression coefficient	<i>p</i>
Age (years)	-0.023	0.009	-0.377	0.0215
BMI	0.038	0.017	0.306	0.0296
FPG	-0.013	0.006	-0.305	0.0529

The dependent variable is ΔHbA1c . The independent variables are age, BMI, and FPG levels. R^2 for the entire model = 0.489

BMI body mass index, *FPG* fasting plasma glucose

that liraglutide effects were mediated by alterations in the expression of genes and proteins involved in lipid metabolism, particularly that of *Acrp30* [14]. In our study as well, LDL-C levels were also significantly decreased and HDL

levels were unchanged after 24 weeks of treatment with dulaglutide (Table 1).

It has been reported that hypoglycemia is a frequently observed adverse event in older patients with type 2 diabetes [15]. The JDS committee recommends reducing concomitant SU doses after initiation of treatment with GLP-1 receptor agonists for proper use of GLP-1 receptor agonists [16]. In our study, hypoglycemia was seen in one patient receiving a SU drug.

Boustani et al. reported that the efficacy of 0.75 mg dulaglutide was similar in elderly and young patients and that the reductions in HbA1c levels at 26 weeks were -1.16% in patients aged ≥ 65 years and -1.10% in patients aged < 65 in phase 3 studies [17]. However, our study demonstrates that old age is useful in predicting the HbA1c-lowering effect of switching from sitagliptin to dulaglutide in clinical practice.

Table 5 Multiple regression analysis of the relationship between ΔFPG and other associated variables

Risk factors	Regression coefficient	Standard error	Standardized regression coefficient	<i>p</i>
Duration of diabetes	-0.305	0.344	-0.161	0.3813
DBP	0.020	0.264	0.014	0.9399
FPG	-0.589	0.166	-0.541	0.0013

The dependent variable is ΔHbA1c . The independent variables are duration of diabetes, DBP, and FPG levels. R^2 for the entire model = 0.367

DBP diastolic blood pressure, *FPG* fasting plasma glucose

Table 6 Multiple regression analysis of the relationship between Δ LDL-C and other associated variables

Risk factors	Regression coefficient	Standard error	Standardized regression coefficient	<i>p</i>
AST	0.081	0.311	0.059	0.7968
ALT	− 0.342	0.303	− 0.244	0.2670
LDL-C	− 0.514	0.144	− 0.535	0.0012
TG	− 0.080	0.052	− 0.214	0.1360

The dependent variable is Δ LDL-C. The independent variables are AST, ALT, LDL-C, and TG levels. R^2 for the entire model = 0.440

AST aspartate aminotransferase, ALT alanine aminotransferase, LDL-C low-density lipoprotein cholesterol, TG triglycerides

It was reported that the mean changes in HbA1c levels from baseline were -1.69% in the age < 65 /BMI < 25 subgroup; -1.48% in the age < 65 /BMI ≥ 25 subgroup; -1.68% in the age ≥ 65 /BMI < 25 subgroup; and -1.72% in the age ≥ 65 /BMI ≥ 25 subgroup in phase 3 studies of dulaglutide in Japanese diabetes mellitus patients. The changes from baseline levels were not statistically significantly different across the four subgroups [18]. However, our study demonstrates that old age and low BMI are useful in predicting the HbA1c-lowering effect of dulaglutide in clinical practice. The Δ HbA1c was significantly different between younger (< 65 years of age) and elderly groups (≥ 65 years of age) (-0.193 ± 0.410 vs. $-0.815 \pm 0.701\%$, $p = 0.0044$ respectively). However, the Δ HbA1c was not significantly different between non-obese group (BMI < 25) and obese group (BMI ≥ 25) (-0.837 ± 0.821 vs. $-0.463 \pm 0.601\%$, respectively). Furthermore, we demonstrated that the mean changes in HbA1c levels from baseline were $-0.433 \pm 0.586\%$ in the age < 65 /BMI < 25 subgroup; $-0.133 \pm 0.363\%$ in the age < 65 /BMI ≥ 25 subgroup; $-1.08 \pm 0.901\%$ in the age ≥ 65 /BMI < 25 subgroup; and $-0.727 \pm 0.633\%$ in the age ≥ 65 /BMI ≥ 25 subgroup in our study. The changes from baseline were statistically significantly different across the 4 subgroups (one factor ANOVA; $p = 0.0207$).

The difference between our results and those in previous reports may be because of the variation between clinical practice and phase 3 studies.

The major limitation of this study is the small number of subjects evaluated. The short duration of this study may be an additional limitation because the extent of glycemic response may not have been fully elucidated over this time frame. Furthermore, other markers that could have affected HbA1c-level reduction because of switching from sitagliptin to dulaglutide were not measured in this study. These includes waist circumference as a marker of central obesity, markers for the assessment of β -cell function in homeostatic models, and basal DPP-4 activity. Therefore, more subjects

and more detailed clinical parameters are needed in the future to avoid overestimation of the data obtained.

In conclusion, this prospective 24-week study showed that baseline low BMI and old age were significantly useful in predicting the HbA1c-lowering effect of switching from sitagliptin to dulaglutide. For elderly patients with type 2 diabetes mellitus, weekly dulaglutide, which is available in an easy-to-inject device and has a low incidence of hypoglycemia, may be a beneficial treatment option. Long-term analysis of a larger patient population is warranted to confirm these findings.

Author contributions TI contributed to the conception and design of the work. TI, TK, and MY contributed to the acquisition, analysis, and interpretation of data for the work. TI drafted the manuscript. TI, TK, and MY critically revised the manuscript for important intellectual content. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Compliance with ethical standards

Ethics approval All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later revision.

Informed consent Informed consent or substitute for it was obtained from all patients for being included in the study.

Conflict of interests The authors declare that they have no competing interests.

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