

Dulaglutide as an Add-on to Insulin in Type 2 Diabetes; Clinical Efficacy and Parameters Affecting the Response in Real-World Practice

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Jiwoo Lee
Yun Kyung Cho
Hwi Seung Kim
Chang Hee Jung
Joong-Yeol Park
Woo Je Lee

Department of Internal Medicine, Asan
Medical Center, University of Ulsan
College of Medicine, Seoul, Republic of
Korea

Purpose: For patients with type 2 diabetes (T2DM) who remain above their glycemic target on insulin therapy, a combination of insulin and a glucagon-like peptide 1 receptor agonist has been recommended. However, few studies have been conducted to determine the clinical efficacy and parameters affecting the response to this combination in a real-world setting. This study aimed to investigate the clinical efficacy and parameters affecting the glycemic response to dulaglutide as an add-on to insulin therapy for T2DM in a real-world clinical setting.

Patients and methods: A retrospective study was performed in 120 patients with T2DM who had initiated dulaglutide as an add-on to insulin therapy between January 2017 and December 2018. After 6 months of treatment, the change in glycated hemoglobin (HbA1c) was evaluated. Multiple linear regression analysis was used to determine the parameters affecting the therapeutic response to dulaglutide.

Results: The mean age of the patients was 55.1 years and 57.5% were male. The mean baseline HbA1c, body mass index, and duration of diabetes were 9.1%, 27.5 kg/m², and 17.2 years, respectively. The change in HbA1c between baseline and 6 months was -0.97% (95% confidence interval [CI]: -1.28 to -0.66%, $P<0.001$), the change in body weight was -2.05 kg (95% CI: -2.93 to -1.17 kg, $P<0.001$), and the change in total daily insulin dose was -11.67 IU (95% CI: -14.55 to -8.78 IU, $P<0.001$). In multiple linear regression analysis, higher baseline HbA1c was associated with a greater reduction in HbA1c. The most frequent adverse events were gastrointestinal symptoms, but these were well-tolerated.

Conclusion: Dulaglutide treatment in combination with insulin resulted in a significant improvement in HbA1c and body weight over a 6-month period in a real-world clinical setting. Higher baseline HbA1c was associated with a good clinical response.

Keywords: dulaglutide, glucagon-like peptide-1 receptor agonist, insulin therapy, glycemic control, diabetes mellitus

Introduction

Patients with type 2 diabetes (T2DM) who do not achieve their glycemic goal by taking an oral anti-diabetic drug (OAD) alone eventually require additional therapy with insulin or a glucagon-like peptide-1 receptor agonist (GLP-1 RA). The addition of insulin to OADs has been the conventional strategy for the initiation of injectable therapy. In the first instance, basal insulin administration is usually commenced and then, if the patient's HbA1c concentration remains above their target, short-acting insulin or an alternative premixed insulin administration regimen is instituted.¹ However, many patients that commence insulin or intensify their

Correspondence: Woo Je Lee
Department of Internal Medicine, Asan
Medical Center, University of Ulsan College
of Medicine, 88, Olympic-Ro 43-Gil,
Songpa-Gu, Seoul 05505, Republic of Korea
Tel +82-2-3010-5882
Fax +82-2-2045-4034
Email lwjatlas@gmail.com

insulin treatment regimen do not reach their glycemic target, and are more likely to experience hypoglycemic events and weight gain.²

GLP-1 RAs are appropriate agents for the management of T2DM, given their potent effects to reduce blood glucose and body weight, and the low risk of hypoglycemia associated with their use.³ Therefore, there has been interest in using GLP-1 RAs as add-ons to insulin therapy because of their complementary effects on glycemic control, body weight, and hypoglycemic risk.^{4,5}

Dulaglutide is a GLP-1 RA that is approved for once-weekly administration for the treatment of T2DM in many countries.⁶ The efficacy and safety of the addition of dulaglutide to insulin therapy have been assessed in several component studies of the Assessment of Weekly Administration of LY2189265 in Diabetes (AWARD) trial.^{7–9} However, few studies have investigated the efficacy of dulaglutide combined with insulin in a real-world setting. Moreover, studies that have aimed to determine the clinical factors associated with the efficacy of the combination of dulaglutide and insulin therapy have been few in number. Therefore, we aimed to determine the efficacy and clinical parameters affecting the glucose-lowering effect of dulaglutide as an add-on to insulin therapy in a real-world clinical setting.

Materials and Methods

Study Population

We retrospectively reviewed the data associated with patients who initiated dulaglutide treatment as an add-on to insulin between January 2017 and December 2018 at Asan Medical Center (Seoul, Republic of Korea). Of these, patients who continued combined dulaglutide and insulin therapy for at least 6 months and self-reported high levels of compliance were included. Initially, 166 patients were identified. Of these, patients who were lost to follow-up ($n=13$), stopped taking dulaglutide due to adverse events within the first month ($n=14$), used short-acting GLP-1 RAs prior to dulaglutide ($n=9$), self-reported low levels of compliance with therapy ($n=6$), were hospitalized for example, for diabetic foot infection treatment, kidney transplantation, or pancreaticoduodenectomy ($n=3$), or stopped administering insulin ($n=1$) were excluded. Therefore, 120 patients who recorded regular dulaglutide and insulin use for at least 6 months were included in the analysis.

The present study was conducted in accordance with the principles of the Declaration of Helsinki and Korean Good

Clinical Practice, and was approved by the Institutional Review Board of Asan Medical Center (IRB No. 2018-1050).

Assessment of Treatment Efficacy

Baseline data, including age, sex, body weight, body mass index (BMI), duration of diabetes, total daily insulin dose, presence of hypertension or dyslipidemia, and use of medication, were collected through a review of electronic medical records. Laboratory measurements were also performed at baseline: HbA1c, fasting plasma glucose (FPG), postprandial 2 hr plasma glucose (PP2), fasting C-peptide, total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), triglycerides (TG), creatinine, glomerular filtration rate (GFR), and liver enzymes. After 3 months (± 4 weeks) and 6 months (± 4 weeks) of dulaglutide treatment, all these measurements were repeated.

The primary objective of the study was to evaluate the efficacy of once-weekly dulaglutide as an add-on to insulin over 6 months by assessing the change in HbA1c from baseline. The secondary objectives of the study were to evaluate the changes in FPG, body weight, and total daily insulin dose between baseline and 6 months. These parameters were also evaluated after 3 months of treatment.

Assessment of Clinical Parameters and Adverse Events

Parameters affecting the glycemic response to dulaglutide treatment were assessed using multiple linear regression analysis. For the subgroup analysis, the changes in HbA1c in groups of patients were analyzed according to age, baseline HbA1c, BMI, and duration of diabetes.

We also reviewed the adverse events recorded in the medical records of each patient who underwent dulaglutide and insulin treatment.

Statistical Analysis

Continuous variables are expressed as the mean \pm standard deviation (SD) and categorical variables are expressed as percentages. Student's *t*-tests were used to compare the means of continuous variables, and the χ^2 test was used for categorical variables. The paired *t*-test was used to compare the changes in HbA1c, FPG, body weight, and total daily insulin dose between baseline and 6 months. A linear mixed model was used to analyze repeated measurements. Linear regression analysis was conducted to assess the relationships between clinical parameters and

the therapeutic efficacy of dulaglutide. All statistical analyses were performed using SPSS software version 21.0 for Windows (IBM, Inc., Armonk, NY). $P < 0.05$ was considered to represent statistical significance.

Results

Baseline Characteristics

The baseline characteristics of the participants are shown in Table 1. Their mean age was 55.1 ± 11.0 years and 57.5% of them ($n=69$) were male. The mean baseline HbA_{1c}, BMI, and duration of diabetes were $9.1 \pm 1.7\%$, 27.5 ± 3.6 kg/m², and 17.2 ± 8.3 years, respectively. The mean total daily insulin dose at baseline was 47.8 ± 25.6 international units (IU). The patients were categorized into two subgroups according to their change in HbA_{1c} between baseline and 6 months ($\geq 1\%$ vs $< 1\%$). Those who showed a reduction in HbA_{1c} $\geq 1\%$ were defined as

“responders”. When the baseline characteristics of responders and non-responders were compared, the responders had significantly higher HbA_{1c} and FPG.

Before initiating dulaglutide therapy, most of the patients (85.8%) had been treated with a combination of insulin and OADs. In this subgroup, 40.0% of the patients had been treated with basal insulin plus OADs ($n=48$), and 24.2% had been treated with both basal and prandial insulin, plus OADs ($n=29$). After the initiation of dulaglutide, 50.8% ($n = 61$) of the patients were taking insulin plus metformin, and 33.3% ($n = 40$) were taking insulin, metformin, and sulfonylurea (Supplementary Tables 1 and 2).

Efficacy of Dulaglutide as an Add-on to Insulin Therapy

After 6 months of taking dulaglutide, HbA_{1c}, FPG, body weight, and total daily insulin dose had all significantly

Table 1 Baseline Characteristics of the Study Participants, Classified According to Their Change in HbA_{1c}

Parameter	All Participants (n=120)	HbA _{1c} Change		
		$\geq 1\%$ (n = 56)	$< 1\%$ (n = 64)	P value
Age, yr	55.1 ± 11.0	57.2 ± 11.1	53.3 ± 10.7	0.052
Sex, male	69 (57.5)	35 (62.5)	34 (53.1)	0.300
T2DM duration, yr	17.2 ± 8.3	17.2 ± 9.2	17.1 ± 7.4	0.936
Body mass index, kg/m ²	27.5 ± 3.6	28.1 ± 3.7	26.9 ± 3.5	0.062
Total daily insulin dose, IU	47.8 ± 25.6	49.0 ± 30.2	46.7 ± 21.0	0.637
HbA _{1c} , %	9.1 ± 1.7	10.0 ± 1.4	8.3 ± 1.5	< 0.001
FPG, mg/dL	168.6 ± 64.7	183.2 ± 68.5	155.9 ± 58.8	0.021
PP2, mg/dL ^a	253.6 ± 92.5	251.7 ± 98.2	255.9 ± 86.3	0.847
Fasting C-peptide, ng/mL ^a	2.1 ± 1.6	2.0 ± 1.3	2.2 ± 1.8	0.697
Total cholesterol, mg/dL	154.9 ± 40.2	155.8 ± 44.9	154.2 ± 35.9	0.834
Triglycerides, mg/dL	169.2 ± 92.5	176.9 ± 95.2	162.6 ± 90.5	0.405
HDL-cholesterol, mg/dL	45.5 ± 11.3	44.7 ± 11.6	46.2 ± 11.0	0.473
LDL-cholesterol, mg/dL	98.0 ± 31.4	101.9 ± 35.8	96.5 ± 27.0	0.367
BUN, mg/dL	18.8 ± 8.9	19.3 ± 10.6	18.4 ± 7.1	0.609
Creatinine, mg/dL	0.98 ± 0.36	1.01 ± 0.40	0.94 ± 0.31	0.282
eGFR, mL/min/1.73 m ²	82.7 ± 23.7	80.8 ± 25.4	84.4 ± 22.2	0.416
AST, IU/L	26.2 ± 14.1	28.5 ± 17.0	24.2 ± 10.6	0.096
ALT, IU/L	27.6 ± 20.1	31.0 ± 23.3	24.6 ± 16.5	0.081
Urine ACR, mg/g Cr ^a	625.7 ± 1621.5	835.9 ± 2167.8	439.7 ± 877.2	0.214
Dulaglutide dose, n				0.024
0.75 mg	38 (31.7)	12 (21.4)	26 (40.6)	
1.5 mg	82 (68.3)	44 (78.6)	38 (59.4)	
Hypertension	73 (60.8)	34 (60.7)	39 (60.9)	0.980
Dyslipidemia	101 (84.2)	46 (82.1)	55 (85.9)	0.570

Notes: Data are presented as means \pm standard deviation or as n (%). ^aPP2 concentrations were not available for 42 participants. Fasting C-peptide levels were not available for ten patients. Urine ACRs were not available for five participants.

Abbreviations: T2DM, type 2 diabetes mellitus; IU, international units; FPG, fasting plasma glucose; PP2, postprandial 2 h glucose; HDL/LDL, high-density/low-density lipoprotein; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; AST/ALT, aspartate/alanine aminotransferase; ACR, albumin/creatinine ratio.

decreased. At this time point, the change in HbA1c was -0.97% (95% confidence interval [CI]: -1.28 to -0.66% , $P < 0.001$; [Figure 1A](#)), and the change in FPG was -19.88 mg/dL (95% CI: -32.82 to -6.95 mg/dL, $P = 0.003$; [Figure 1B](#)). The change in body weight was -2.05 kg (95% CI: -2.93 to -1.17 kg, $P < 0.001$; [Figure 1C](#)), and the change in total daily insulin dose was -11.67 IU after 6 months of treatment (95% CI: -14.55 to -8.78 IU, $P < 0.001$; [Figure 1D](#)). Of the patients, 23.3% achieved an HbA1c $< 7\%$ during this period ($n = 28$).

There were also significant changes in HbA1c, body weight, and total daily insulin dose between baseline and 3 months (all $P < 0.001$), but not in FPG ($P = 0.071$) ([Supplementary Figure 1](#)).

Clinical Parameters Affecting the Efficacy of Add-on Dulaglutide

To identify the parameters that predict the glucose-lowering effect of dulaglutide, univariate and multiple linear regression analysis of the reduction in HbA1c was

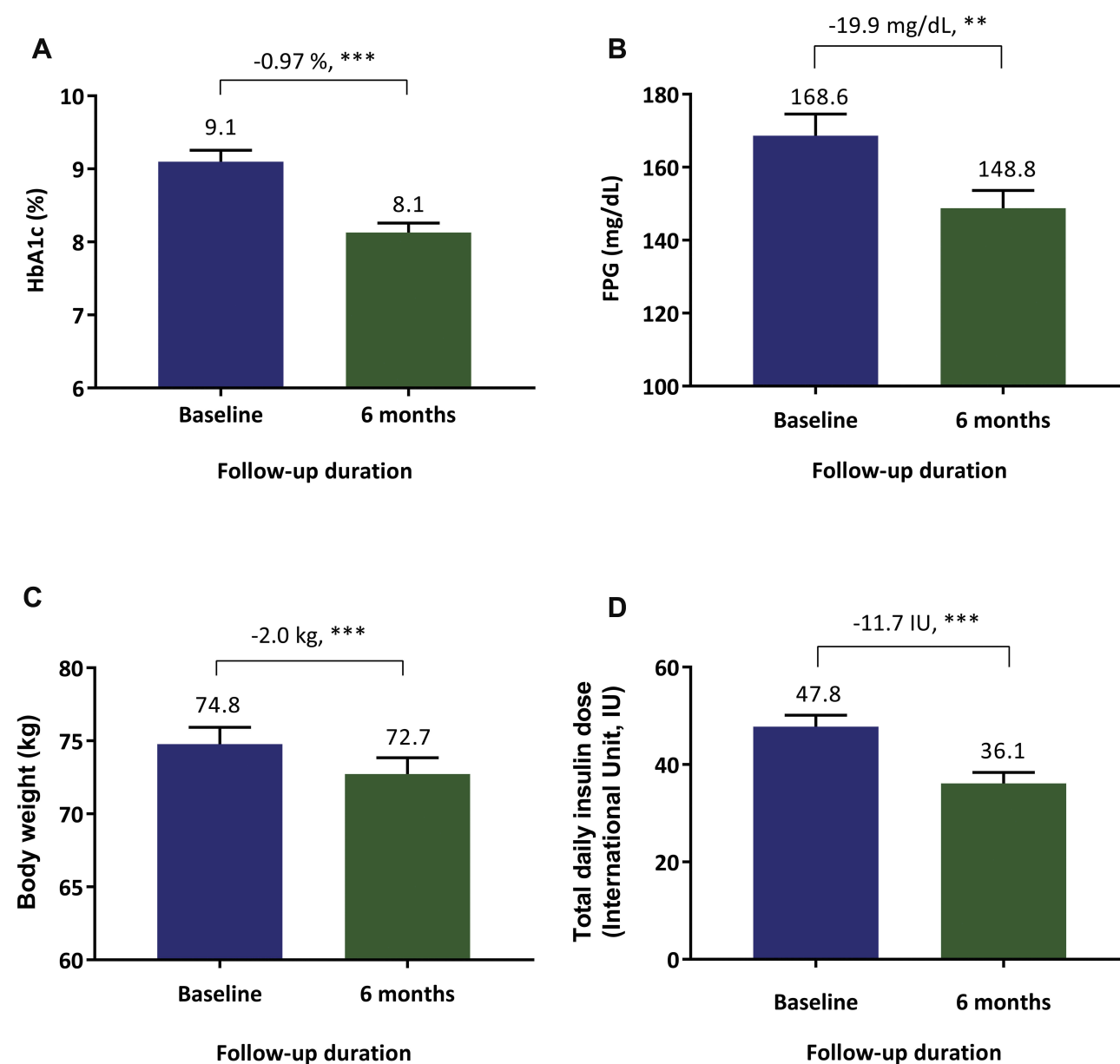


Figure 1 Measures of therapeutic efficacy of add-on dulaglutide over 6 months (A) HbA1c, (B) fasting plasma glucose, (C) body weight, and (D) total daily insulin dose. Data are presented as mean \pm standard error (SE); *** $P < 0.001$ versus baseline; ** $P < 0.01$.

performed. Univariate regression analysis showed that the reduction in HbA1c between baseline and 6 months was associated with higher baseline HbA1c and FPG (Table 2). Similarly, after multiple linear regression analysis, involving adjustment for age, sex, baseline HbA1c, baseline body weight, and the changes in total daily insulin dose, higher baseline HbA1c significantly affected the reduction in HbA1c in patients treated with add-on dulaglutide for 6 months (Table 3). However, age, sex, body weight, and the changes in total daily insulin dose were not associated with the reduction in HbA1c.

Subgroup Analysis of the Efficacy of Dulaglutide as an Add-on to Insulin Therapy

Patients were categorized into the following subgroups: age < 65 years (n = 101) or ≥ 65 years (n = 19); HbA1c < 10.0% (n = 79) or ≥ 10.0% (n = 41); BMI ≤ 25 kg/m² (n = 34) or > 25 kg/m² (n = 86); and DM duration ≤ 15 years (n = 50) or > 15 years (n = 70). HbA1c significantly decreased in the

subgroup with baseline HbA1c ≥ 10.0%, whereas little reduction in HbA1c was identified in patients with baseline HbA1c < 10.0% (2.0% vs 0.5%, $P < 0.001$). In the BMI subgroups of ≤ 25 kg/m² and > 25 kg/m², HbA1c decreased by 0.5% and 1.1%, respectively ($P = 0.088$). However, when the patients were categorized according to age or DM duration, the reductions in HbA1c did not differ between the subgroups (Figure 2).

Adverse Events

The incidences of specific adverse events are shown in Table 4. Adverse events were reported in 36 (31.6%) and 20 patients (16.7%) after 3 and 6 months of dual treatment, respectively. The most common adverse events at both time points were gastrointestinal [30 (26.3%) vs 16 (13.3%)], in particular nausea [(24 (21.1%) vs 12 (10.0%)]]. There were also other gastrointestinal adverse events, including abdominal pain, dyspepsia, and diarrhea. In addition, 2.6% (n = 3) and 0.8% (n = 1) of patients reported hypoglycemia during the first 3 and 6 months of

Table 2 Univariate Linear Regression Analysis of the Reduction in HbA1c

Parameter	Standardized β	95% CI	p value
Age, yr	-0.012	-0.041 to 0.016	0.392
Sex, female	0.430	-0.202 to 1.062	0.181
Baseline HbA1c, %	-0.663	-0.802 to -0.524	< 0.001
Baseline FPG, mg/dL	-0.008	-0.012 to -0.003	0.002
C-peptide, ng/mL	-0.019	-0.234 to 0.196	0.861
Baseline body weight, kg	-0.014	-0.039 to 0.011	0.283
Baseline BMI, kg/m ²	-0.066	-0.152 to 0.021	0.136
T2DM duration, yr	0.008	-0.030 to 0.046	0.674
Total daily insulin dose at baseline, IU ^a	0.001	-0.011 to 0.013	0.868
Changes in total daily insulin dose, IU	0.013	-0.007 to 0.033	0.192
eGFR, mL/min/1.73m ²	0.002	-0.011 to 0.016	0.717
Hypertension	0.191	-0.453 to 0.836	0.558
Dyslipidemia	0.091	-0.772 to 0.954	0.835

Note: ^aChanges in total daily insulin dose were measured between the total daily insulin dose at baseline and the total daily insulin dose after 6 months.

Abbreviations: CI, confidence interval; HbA1c, glycated hemoglobin; FPG, fasting plasma glucose; T2DM, type 2 diabetes mellitus; IU, international units; BMI, body mass index; GFR, glomerular filtration rate.

Table 3 Multiple Linear Regression Analysis of the Reduction in HbA1c

Parameter	Standardized β	95% CI	p value
Age, yr	-0.012	-0.036 to 0.012	0.320
Sex, female	0.460	-0.045 to 0.965	0.074
Baseline HbA1c, %	-0.699	-0.847 to -0.551	< 0.001
Baseline body weight, kg	-0.010	-0.032 to 0.012	0.361
Change in total daily insulin dose, IU ^a	-0.012	-0.028 to 0.005	0.167

Note: ^aChanges in total daily insulin dose were measured between the total daily insulin dose at baseline and the total daily insulin dose after 6 months.

Abbreviations: CI, confidence interval; HbA1c, glycated hemoglobin; T2DM, type 2 diabetes mellitus; IU, international units.

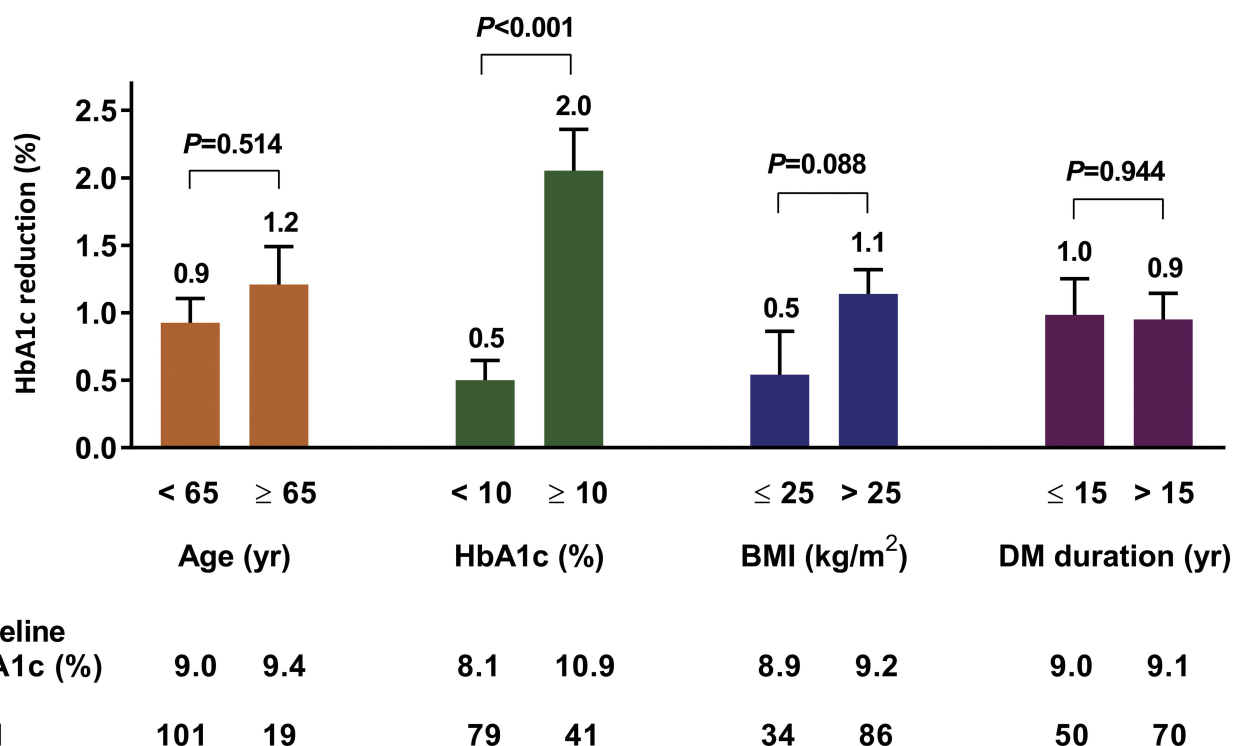


Figure 2 Change in HbA1c between baseline and 6 months in each subgroup of participants.

treatment, but no severe hypoglycemia was reported. Overall, the incidence of adverse events tended to decrease with time.

Discussion

In this analysis of real-world data, the addition of once-weekly dulaglutide to insulin treatment for 6 months was effective in reducing HbA1c, as well as body weight and total daily insulin dose. Although the combination of dulaglutide and insulin was associated with a significant

improvement in HbA1c, irrespective of age, baseline BMI, and duration of diabetes, higher baseline HbA1c did affect the glucose-lowering effect of add-on dulaglutide.

The changes in HbA1c, FPG, body weight, and total daily insulin dose after 6 months of dulaglutide as an add-on to insulin treatment were -0.97% , -19.88 mg/dL, -2.05 kg, and -11.67 IU, respectively. The AWARD-9 trial⁹ compared the effects of adding dulaglutide or placebo with insulin glargine, thereby having a similar design to the present study, because 78.3% of the participants in the present study were administering basal insulin when dulaglutide was added. In the AWARD-9 trial, the mean changes in HbA1c and body weight between baseline and 28 weeks were -1.44% and -2.41 kg, respectively, which are larger than the changes achieved in the present study. This disparity might be explained by real-world factors, such as lower compliance with follow-up and/or medication. In addition, the mean changes in glargine dose was increased in the AWARD-9 trial (13 ± 2 IU), and the decreased changes in total daily insulin dose at 6 months (-11.67 ± 1.46 IU) are also consistent with a smaller reduction in HbA1c than in the clinical trial. Moreover, the percentages of participants achieving an HbA1c $< 7\%$ were 23.3% in the present study, but 66.7% in the AWARD-9 trial. However, in the present study, the baseline HbA1c was higher (9.1%) than in the AWARD-9 trial

Table 4 Adverse Events Recorded

Adverse Event	3 Months (n=114)	6 Months (n=120)
Total n (%)	36 (31.6)	20 (16.7)
Nausea	24 (21.1)	12 (10.0)
Vomiting	0 (0)	0 (0)
Abdominal pain	2 (1.8)	2 (1.7)
Dyspepsia	3 (2.6)	2 (1.7)
Diarrhea	1 (0.9)	0 (0)
Constipation	0 (0)	0 (0)
Hypoglycemia	3 (2.6)	1 (0.8)
Allergic reaction	1 (0.9)	2 (1.7)
Injection site reaction	1 (0.9)	1 (0.8)
Other	1 (0.9)	0 (0.0)

Note: Data are n (%).

(8.4%), which might explain the lower proportion of patients reaching this HbA1c target in the present study.

Overall, however, the results of the present study are consistent with those of previous clinical trials. The DURATION-7 study¹⁰ determined the efficacy of once-weekly exenatide or placebo added to titrated basal insulin in patients with T2DM, and showed a 1% reduction in HbA1c in the exenatide arm after 28 weeks of treatment. The HARMONY-6 trial¹¹ analyzed the efficacy of adding once-weekly albiglutide vs thrice-daily prandial insulin to basal insulin administration. Following 26 weeks of treatment, the change in HbA1c was -0.82% in the albiglutide group. The BEGIN: Victoza Add-On study¹² compared the effects of once-daily liraglutide and once-daily insulin aspart on basal insulin, finding a 0.74% reduction in HbA1c in the liraglutide arm. Finally, the SUSTAIN-5 trial¹³ assessed the efficacy and safety of once-weekly semaglutide in addition to basal insulin. At the end of 30 weeks of treatment, the reductions of HbA1c associated with the administration of 0.5 or 1.0 mg semaglutide were 1.4% and 1.8%, respectively.

One previous real-world study of the use of other GLP-1 RAs in 108 patients has also been conducted, which compared the addition of once-weekly exenatide or once-daily liraglutide to basal insulin.¹⁴ The addition of exenatide reduced HbA1c by 0.7% after 12 months and the change in HbA1c was -0.8% when liraglutide was added to insulin. Furthermore, the addition of exenatide and liraglutide were both associated with 2.3 kg reductions in body weight in this study. These real-world findings were also similar to those of the present study with respect to the reductions in HbA1c and body weight achieved.

We have shown here that patients with a higher baseline HbA1c achieve a larger HbA1c reduction. Consistent results have been reported following subgroup analyses of data from clinical trials and observational studies of dulaglutide administration.^{15–20} In previous studies of the addition of other long-acting GLP-1 RAs, including liraglutide and albiglutide, to insulin, participants with higher baseline HbA1c values also achieved larger reductions in HbA1c.^{11,21} In the present analysis, other factors, such as age, sex, baseline body weight, and changes in total daily insulin dose, did not affect the change in HbA1c achieved. These findings were also consistent with those of previous studies, which showed that dulaglutide treatment lowers blood glucose irrespective of age, sex, duration of diabetes, baseline BMI, and estimated GFR.^{8,15,16,18,22}

The adverse events associated with dulaglutide use reported in this study were similar to those previous

reported.^{23,24} The most commonly reported adverse events were gastrointestinal disorders, including nausea and dyspepsia, but these were tolerated over the period of the study. By contrast, only three hypoglycemic events were reported during the 6 months of the study, and no severe hypoglycemic events. It is important to find the optimal balance between glycemic control and the risk of hypoglycemia in patients using high doses of insulin. Accordingly, the high efficacy and low risk of hypoglycemia associated with the use of dulaglutide alongside insulin may mean that this should be the preferred option for patients requiring a high dose of insulin.

To the best of our knowledge, the present study is the first to determine the efficacy of the addition of dulaglutide to insulin therapy in a real-world setting. Only a few previous studies have demonstrated the efficacy of dulaglutide in a real-world setting,^{17,19,25,26} but these studies mainly compared the efficacy of the combination of dulaglutide and other OADs.

This study had several limitations. First, the 6-month duration of follow-up was relatively short; therefore, we could not investigate the long-term effects of dulaglutide treatment. However, the efficacy of dulaglutide at 26 weeks was similar to that shown at 56 weeks in a previous study.²⁷ Consequently, this duration of follow-up may be sufficient to appropriately assess the efficacy of dulaglutide. Second, various anti-diabetic medications had been used by the participants before the initiation of dulaglutide, and continued to be used alongside dulaglutide, which may have added variation to the efficacy of the add-on dulaglutide. Third, the adverse events recorded were those described in the participants' medical records, so there may have been some missed events. Lastly, only Korean patients were included in the present study; therefore, the results may not be generalizable to other populations.

Conclusion

Once-weekly dulaglutide treatment as an add-on to insulin therapy improved glycemic control, reduced body weight, reduced total daily insulin dose, and was associated with a low risk of adverse events in a real-world situation. Furthermore, baseline HbA1c level was shown to affect the extent of the reduction in HbA1c.

Abbreviations

AWARD, Assessment of Weekly Administration of LY2189265 in Diabetes; BMI, body mass index; CI, confidence interval; FPG, fasting plasma glucose; GFR, glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; HDL-C,

high-density lipoprotein-cholesterol; IU, international units; LDL-C, low-density lipoprotein-cholesterol; OAD, oral anti-diabetic drug; PP2, postprandial 2 hr plasma glucose; SD, standard deviation; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglyceride.

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Disclosure

The authors report no conflicts of interest in this work.

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