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ORIGINAL RESEARCH

Real-World Analysis of Rapid-Acting Insulin Analog Use and Its Blood Glucose Lowering Effect in Patients with Type 2 Diabetes Mellitus: Results from PASSION Disease Registry in Korea

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Purpose: Although rapid-acting insulins (RAIs) are used frequently in Korean clinical settings, evidence on their use is limited. This study explores the pattern and clinical effectiveness of the use of RAIs in Korean patients with type 2 diabetes mellitus (T2DM).

Patients and Methods: This non-interventional, observational study enrolled patients (aged >18 years) with T2DM who were prescribed RAIs. The pattern of use and effectiveness of RAI analogs were evaluated over 6 months.

Results: A total of 299/451 patients were analyzed. Approximately 90% (n/N=270/299) of the patients received insulin glulisine, which significantly reduced their levels of glycated hemoglobin (HbA1c: n=270, mean± standard deviation [SD]; −1.16±6.02%, p=0.0017), fasting plasma glucose (n=40; mean±SD: −54.9±90.89 mg/dl, p=0.0005), and post prandial blood glucose (n=35, mean±SD: −89.46± 105.68 mg/dl, p<0.0001) at 6 months, with a corresponding increase in body weight (BW) (n=197, mean±SD:1.45±3.64 kg, p<0.0001). At 6 months, more patients receiving an intensive regimen (basal insulin+≥2 RAI injections/day) had HbA1c <7% than those receiving a non-intensive regimen (basal insulin+1 RAI injection/day) (20.69% vs 7.46%; p=0.0333); the corresponding reduction in HbA1c was also higher in patients receiving the intensive regimen (p<0.0001). About one-fourth patients (n/N=22/95) were switched to the intensive regimen (from 1 to ≥2 RAI injections/day), and only 4.41% (n/N=9/204) of the patients were switched to 1 RAI injection/day. The patients receiving the intensive regimen showed higher levels of HbA1c reductions (mean±SD: −1.27±1.96%) compared with the maintenance group-1 RAI injection/day (mean±SD: −0.72±1.66%) (p=0.0459), without a significant increase in BW and body mass index.

Conclusion: The insulin glulisine intensification regimen showed glycemic target achievement and can be considered a therapeutic tool in the management of T2DM patients.

Keywords: glycated hemoglobin, insulin glulisine, intensification, RAI analogs

Introduction

Diabetes affects more than 463 million people globally, and its prevalence is on the rise. In Korea, approximately 3.69 million people are affected by diabetes,[1] with an increasing number of associated microvascular and macrovascular

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complications causing a corresponding rise in morbidity and mortality.[2,3] Furthermore, diabetes lowers quality of life and contributes largely to disability-adjusted life years.[4,5]

According to the Diabetes fact sheet by Korean Diabetes Association (2018), over half of Korean patients with diabetes (52.6%) reached the glycated hemoglobin (HbA1c) target of <7%, whereas only one-fourth (25.1%) of the patients reached the HbA1c <6.5% target.[6] However, almost half of the patients with diabetes in Korea (43.1%) were not receiving treatment, and among those patients with diabetes who received treatment, oral hypoglycemic agents (OHAs) (51.5%) were the most common, whereas only 5.2% patients were using insulin.[6] Hence, there is a substantial gap between the current management of diabetes in Korea and the internationally accepted guideline recommendations by the American Association of Clinical Endocrinologists (AACE) and American Diabetes Association (ADA).[7–10]

Due to the progressive nature of diabetes, if glycemic targets are not achieved by OHA monotherapy (usually with metformin), the guidelines recommend intensification of treatment with a combination of OHAs or therapies with different mechanisms of action (including insulin and glucagon-like peptide-1 receptor agonist [GLP-1 RA], following step-wise intensification of therapy).[11–13]

Insulin could be initiated for treatment of type 2 diabetes mellitus (T2DM) by adding basal or premixed (biphasic, once-daily or twice-daily) or once-daily co-formulating insulin (composed of insulin degludec and insulin aspart), alone or in combination with GLP-1 RA or in combination with other OHAs.[14,15] If patients fail to achieve glycemic goals after optimal dose titration, it is advised to intensify insulin therapy with premixed insulin (twice/thrice daily), prandial insulin (basal plus or basal bolus using rapid-acting insulin [RAI] or short-acting insulin [SAI]) with the largest meal of the day, or GLP-1 RA. Previous clinical studies have demonstrated the glycemic effects of RAI with or without basal insulin use in a similar real-world setting.[16,17]

In Korea, a basal insulin-based combination of OHAs or RAIs is commonly initiated to achieve or sustain a glycemic target in patients with T2DM. Although RAIs are frequently prescribed in clinical settings in Korea, the literature available about their effect on glycemic control is limited. Our study aimed to explore the effectiveness and clinical implications of RAIs in Korea.

Patient and Methods

Study Objectives and Design

The primary objective of the study was to examine the pattern of use of RAI analogs in Korean patients with T2DM (type, frequency, dose, type of combination, and change in prescription over 6 months). Several other parameters were also evaluated, including the effectiveness of RAI analogs as assessed by changes in HbA1c, fasting plasma glucose (FPG), postprandial plasma glucose (PPG), and blood glucose, after 6 months of treatment. In addition, the study assessed changes in doses and number of injections/day; the percentage of patients achieving the target HbA1c (<7%); and changes in lipid profile, waist circumference, body weight (BW), and body mass index (BMI) after 6 months of treatment. The effects of insulin intensification were also assessed by measuring the impact of daily injection times.

Study Design

This multicenter, non-interventional, prospective observational study was conducted from July 2008 to March 2011 including patients with T2DM who received RAIs. The bipartite study had a cross-sectional regimen to analyze the pattern of RAI analogs and a longitudinal regimen to assess the blood glucose lowering effect of RAI analogs after 6 months in patients with diabetes. The duration of the treatment and observational period was 15 months and 6±1 months, respectively.

Korean men or women aged >18 years with T2DM who were newly prescribed with a RAI analog and willing to sign the data release consent form were enrolled in the study. Patients having any contraindication to insulin treatment were excluded.

Data Collection

Study data were collected at baseline (Visit 1), 3 months (Visit 2), and 6 months (Visit 3; last observation carried forward [LOCF]). Data collected during the study visits included demographic characteristics (age, gender); anthropometric data (weight, waist); disease characteristics (diabetes duration, diabetes-related complications); comorbidities, including

dyslipidemia and baseline treatments (OHAs, insulin); details of RAI analogs (total daily dose, daily injection frequency, intensification of injection per day); and measurements of glycemic parameters (HbA1c, FPG, PPG).

Statistical Analysis

Sample Size Calculation

In Korea, health insurance data show that more than 4 million people are affected by T2DM, and according to the Intercontinental Marketing Statistics data, 12% of people with diabetes who use insulin are treated with RAI analogs. Assuming that at least 10% of patients with T2DM are users of the RAI analog, minimum 30 patients using the RAI analog and 300 patients using any RAI analog were estimated to be required because of normality. Considering 30% dropout, 430 patients were estimated to be enrolled in the study.

Data Analysis

Data were summarized using descriptive analyses. Analysis of covariance (ANCOVA) was performed to evaluate the difference in clinical parameters (HbA1c, FPG, PPG, waist circumference, lipid profile, BMI, and BW) between Visit 1 and Visit 3 among the groups. Paired *t*-test was used to analyze the data in the groups using insulin glulisine. In the absence of data after Visit 2, the LOCF method was used for analysis at Visit 3. Response rates by type of prescription were analyzed using Chi-square test or Fisher's exact test. The difference in variation of daily injection frequency among RAI analogs was analyzed with repeated measures ANCOVA. All analyses were carried out with SAS® 9.2 (SAS Institute, Inc., Cary, NC).

An analysis based on the pattern of RAI intensification was performed by comparing patients receiving 1 RAI injection/day versus ≥2 RAI injections/day because there was an apparent lack of effectiveness with basal-plus intensification with 1 injection/day. The clinical effects were also compared between patients continuing with the 1 RAI injection/day regimen (non-intensive regimen) and those switching to ≥2 RAI injections/day regimen (intensive regimen). This analysis was conducted only for those patients receiving glulisine as it was the most commonly prescribed RAI.

Results

Patient Disposition and Characteristics

A total of 451 patients were enrolled in the study at 23 sites across Korea, of which. 299 patients were analyzed. Details of the patients, RAI type and treatment regimen are presented in Figure 1. The demographic and clinical characteristics at baseline according to intensification of the insulin injection criteria and according to type of insulin are presented in Table 1 and Supplementary Table 1, respectively.

Effects of Insulin Glulisine on Glycemic Indicators and Body Weight

Insulin glulisine significantly improved HbA1c, FPG, and PPG levels 2 hours after meal levels from baseline to 6 months. However, at 6 months, BW increased significantly (Table 2).

HbA1c Levels and Changes in Body Weight in the Intensive Group (Basal Insulin+≥2 RAI Injection/Day) vs the Non-Intensive Group (Basal Insulin+1 RAI Injection/Day)

The proportion of patients with HbA1c <7% at 6 months was higher in the intensive regimen group compared with the non-intensive regimen group (20.69% vs 7.46%, p=0.0333 [Chi-square test]). The proportion of patients with HbA1c ≥7% was 72.41% vs 79.10% in intensive vs non-intensive regimen. The extent of HbA1c reduction at 6 months was significantly higher in the intensive regimen group compared with the non-intensive regimen group (mean±SD difference: −1.41±1.97% vs −0.64±1.47%, p<0.0001). The corresponding increase in BW from baseline to 6 months in the intensive vs non-intensive groups was 0.87±3.2 kg vs 1.51±4.43 kg, p=0.5079 (Table 3).

Intensification of RAI Injection

Out of 299 patients, 95 were on 1 RAI injection/day and 204 were on ≥2 RAI injections/day. About one-fourth (n/N=22/95, 23.16%) of the patients were switched to an intensified injection schedule (from 1 RAI injection/day to ≥2 RAI

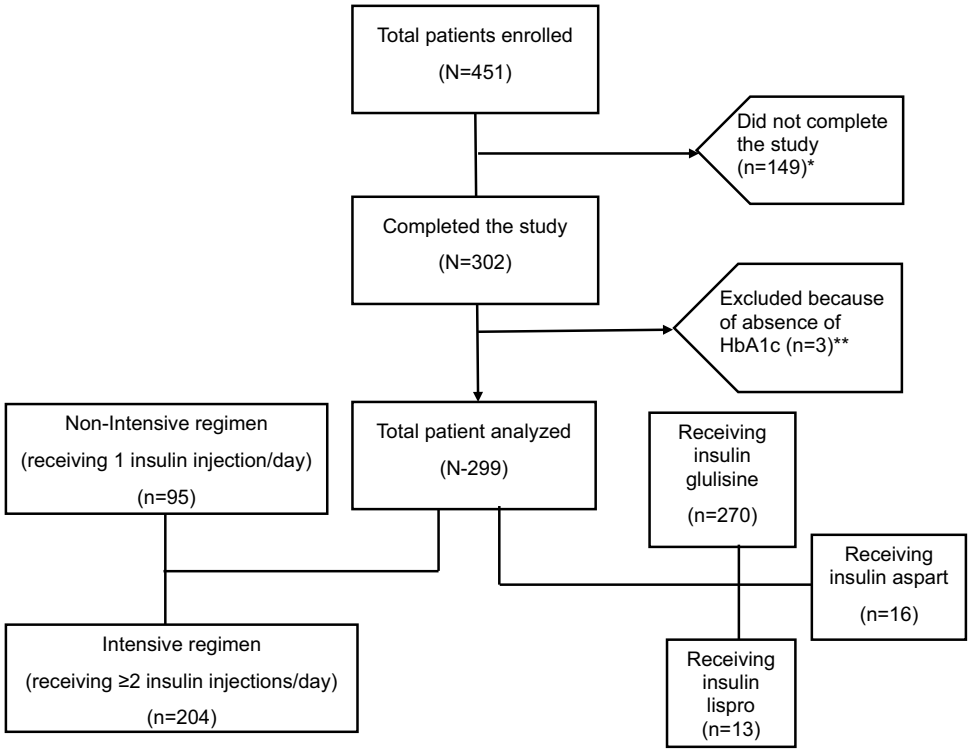

Figure 1 Selection of the study population. *Overlapped patient, n=1; patient administered prior to the contract date, n=1; written consent form unavailable, n=3; inclusion criteria violation, n=59; contents of investigation unclear, n=32; HbA1c not available, n=53. **Three patients did not have HbA1c measurements, as they were not administered insulin or oral hypoglycemic agents at Visit.
Abbreviations: HbA1c, glycated hemoglobin; n, number of patients analyzed; N, total number of patients.

injections/day), whereas 64 (67.37%) maintained the dose as 1 RAI injection/day. In other group, only 4.41% (n/N=9/204) of the patients were switched to a lesser injection schedule (≥2 RAI injections/day to 1 RAI injection/day), whereas 157 (76.96%) maintained the dose as ≥2 RAI injections/day. RAI was not injected in some patients since Visit 1 Most patients were maintained on their initial RAI regimen during the 6 months.

In both the maintenance (1 RAI injection/day) and intensified (RAI 1/day→RAI ≥2/day) groups, HbA1c levels reduced significantly from baseline to 6 months. In maintenance group, HbA1c (mean±SD) at visit 1 was 9.44±1.65 and at 6 months 8.72±1.53 with p value 0.0010 (paired *t*-test). In intensified group, HbA1c (mean±SD) at visit 1 was 9.24 ±1.52 and at 6 months 7.96±1.26 with p value 0.0062 (paired *t*-test)., The decrease in HbA1c levels was greater in the intensified injection group compared with the maintenance group (N=64, mean±SD: −0.72±1.66 vs N=22, Mean±SD: −1.27±1.96; p=0.0459[ANCOVA]). At 6 months, the increase in BW and BMI were not significantly different between the maintenance and intensified groups (mean±SD BW difference: 1.41±2.92 kg vs 2.05±5.11 kg, p=0.6090; mean±SD BMI difference: 0.54±1.15 kg/m^2 vs 0.75±1.93 kg/m^2, p=0.6669 [Supplementary Table 2], respectively).

Discussion

In this study, we examined the pattern of the use of RAI analogs in Korean patients with T2DM and the effects of RAI analogs on glycemic indicators at 6 months. Among the RAI analogs prescribed in this study, the most common (~90%) was insulin glulisine. Addition of insulin glulisine was effective in lowering glycemic indicators considerably at the end of 6 months. Moreover, an intensive regimen of basal insulin+glulisine helped in achieving the target HbA1c in more patients compared with the non-intensive regimen of basal insulin+glulisine. Although the use of RAI was associated with an increase in BW, intensification of RAI did not accelerate the increase.

In the present study, nearly half of the patients (49%) had micro- and macro-vascular complications. Type 2 diabetes is the leading cause of micro- and macro-vascular complications with a high prevalence across the globe.[18] These complications could be lowered by focusing on long-term glycemic control, using early insulin therapy, or optimization

Table 1 Demographic and Clinical Characteristics at Baseline According to Intensification of Insulin Injection

Parameter		RAI 1/Day N=95	RAI ≥2/Day N=204	Total N=299	p-value
Gender	Male	42 (44.21)	114 (55.88)	156 (52.17)	0.0555[a]
	Female	53 (55.79)	90 (44.12)	143 (47.83)	
DM duration (years)	Mean±SD	9.96±7.22	7.67±7.51	8.31±7.49	
	Min~Max	0.17~24.00	0.08~50.00	0.08~50.00	
	<4 years	14 (14.74)	46 (22.55)	60 (20.07)	
	≥4years ~ <8years	10 (10.53)	41 (20.10)	51 (17.06)	
	≥8years ~ <12years	8 (8.42)	25 (12.25)	33 (11.04)	
	≥12years	22 (23.16)	27 (13.24)	49 (16.39)	
DM complications	Yes	55 (57.89)	90 (44.12)	145 (48.49)	0.0265[b]
	No	40 (42.11)	114 (55.88)	154 (51.51)	
	Total	95 (100.00)	204 (100.00)	299 (100.00)	
DM complications overlapped	Diabetic Retinopathy	25 (26.32)	42 (20.59)	67 (22.41)	0.26881[b]
	Diabetic Neuropathy	37 (38.95)	55 (26.96)	92 (30.77)	0.03651[b]
	Diabetic Nephropathy	24 (25.26)	31 (15.20)	55 (18.39)	0.03641[b]
	Micro-Albuminuria	17 (17.89)	16 (7.84)	33 (11.04)	0.00981[b]
	CVD (angina/MI/CHF/Stroke)	10 (10.53)	18 (8.82)	28 (9.36)	0.63801[b]
	PVD	2 (2.11)	0 (0.00)	2 (0.67)	0.10022[c]
Comorbidity disease	Yes	67 (70.53)	120 (58.82)	187 (62.54)	0.0516[b]
	No	28 (29.47)	84 (41.18)	112 (37.46)	
	Total	95 (100.00)	204 (100.00)	299 (100.00)	
Comorbidity disease overlapped	Hypertension (>130/80 mmHg)	37 (38.95)	74 (36.27)	111 (37.12)	0.6560[b]
	Dyslipidemia				
	Total cholesterol (6.1 mmol/L)	7 (7.37)	18 (8.82)	25 (8.36)	0.6721[b]
	LDL (2.5 mmol/L)	19 (20.00)	27 (13.24)	46 (15.38)	0.1312[b]
	HDL (male: <1.0 mmol/L, female: <1.2 mmol/L)	36 (37.89)	42 (20.59)	78 (26.09)	0.0015[b]
	TG (>1.6 mmol/L)	32 (33.68)	38 (18.63)	70 (23.41)	0.0042[b]
	Other	18 (18.95)	16 (7.84)	34 (11.37)	0.0049[b]

Notes: All values are n (%) unless specified otherwise. [a]t-test; [b]Chi-square test; [c]Fisher's Exact test.

Abbreviations: CHF, congestive heart failure; CVD, cardiovascular disease; DM, diabetes mellitus; HDL, high density lipoprotein; LDL, low density lipoprotein; MI, myocardial infarction; N, number of patients analyzed; PVD, peripheral vascular disease; RAI, rapid-acting insulin; SD, standard deviation; TG, triglyceride.

of insulin regimens.[19] This involves targeting short-term (FPG and PPG) and long-term (HbA1c) measures of glucose levels with special attention to indicators of overall glycemic control (PPG and HbA1c). In our study, we found that insulin glulisine acted on all glycemic indicators and reduced the levels significantly at 6 months in the overall study population. Similar findings have been reported with RAI analogs in other studies.[20–23]

Table 2 Changes in HbA1c, FPG, PPG, and Body Weight with Use of Insulin Glulisine

	Glycemic Indicators N=270									
	HbA1c (%)		FPG (mg/dl)		PP2BG (mg/dl)		PP2PG (mg/dl)		BW (kg)	
	n	Mean±SD	n	Mean±SD	n	Mean±SD	n	Mean±SD	n	Mean±SD
Visit 1	270	9.56±1.98	77	203.92±85.55	66	312.67±104.69	46	245.11±86.65	226	63.47±11.07
Visit 2	204	8.90±9.19	44	127.93±48.39	35	218.37±85.59	81	180.75±86.59	189	64.03±11.03
Visit 3	236	8.42±6.16	48	141.56±62.96	46	192.37±66.21	68	199.68±84.45	180	64.94±11.21
Visit 3 (LOCF)	270	8.40±5.79	68	139.76±59.05	62	200.84±68.03	99	188.94±82.89	200	64.80±11.17
Visit 3 (LOCF) − Visit 1	270	−1.16±6.02	40	−54.9±90.89	35	−89.46±105.68	31	−40.65±115.72	197	1.45±3.64
p-value[a]	0.0017		0.0005		<0.0001		0.0599		<0.0001	

Notes: Visit 1=baseline, Visit 2=3 months, Visit 3=6 months. [a]p-value of paired *t*-test between Visit 1 and Visit 3 (LOCF) group.
Abbreviations: BW, body weight; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; LOCF, last observation carried forward; n, number of patients with non-missing values at the Visit; N, number of patients analyzed; PP2BG, postprandial blood glucose levels 2 hours after meal; PP2PG, postprandial plasma glucose levels 2 hours after meal; SD, standard deviation.

Table 3 Change in HbA1c and Body Weight Over 6 Months in the Intensive vs Non-Intensive Group

	Basal Insulin+1 Injection/Day Glulisine N=67		Basal Insulin+≥2 Injection/Day Glulisine N=87		Total (Basal Insulin +Glulisine) N=154		p-value
	n	Mean±SD	n	Mean±SD	n	Mean±SD	
Change in HbA1c (%) over 6 months							
Visit 1	67	9.40±1.41	87	9.23±2.17	154	9.30±1.88	0.5614[a]
Visit 2	52	10.56±12.70	55	7.90±1.54	107	9.20±8.98	0.1279[b]
Visit 3	58	8.67±1.54	81	7.91±1.39	139	8.23±1.50	0.0020[b]
Visit 3 (LOCF)	67	8.76±1.53	87	7.82±1.40	154	8.23±1.53	<0.0001[b]
Visit 3 (LOCF) − Visit 1	67	−0.64±1.47	87	−1.41±1.97	154	−1.07±1.81	<0.0001[b]
Change in body weight (kg) over 6 months							
Visit 1	54	62.31±10.18	64	65.56±11.19	118	64.08±10.81	0.1044[a]
Visit 2	48	62.13±10.71	50	65.82±11.49	98	64.01±11.21	0.6542[b]
Visit 3	49	64.65±11.28	49	66.35±10.42	98	65.50±10.84	0.4837[b]
Visit 3 (LOCF)	52	64.38±11.34	53	66.15±11.07	105	65.28±11.19	0.5079[b]
Visit 3 (LOCF) − Visit 1	49	1.51±4.43	53	0.87±3.2	102	1.18±3.83	0.5079[b]

Notes: Visit 1=baseline, Visit 2=3 months, Visit 3=6 months. [a]p-value *t*-test, [b]p-value ANCOVA analysis.
Abbreviations: HbA1c, glycated hemoglobin; LOCF, last observation carried forward; n, number of patients with non-missing values at the Visit; N, number of patients analyzed; SD, standard deviation.

Clinical guidelines recommend intensifying insulin therapy with RAI analogs (single/multiple boluses of prandial injection or as a part of premixed insulin) as up-titration of basal insulin therapy eventually becomes insufficient for maintaining glycemic targets.[9–11,24] In our study, a similar prescription pattern of insulin analogs was selected, wherein the treating physician initiated the insulin therapy with different RAI analogs to achieve glycemic control. We found that

intensification of basal insulin using 1 RAI injection/day did not prove effective; therefore, it was intensified to ≥2 RAI injections/day. Approximately 77% patients receiving ≥2 RAI injections/day were maintained in the same regimen and down-titrated in only 4% patients. Thus, treatment persistence was more in patients in the intensified injection regimen compared with those who were maintained on once daily RAI administration.

One of the major concerns regarding the initiation of insulin or intensification of an insulin regimen is weight gain.[24] Weight gain during insulin therapy could be attributed to anabolic effects of insulin, increase in appetite, and reduction of glycosuria.[25] A study that investigated the use of RAI analogs reported weight gain in patients receiving insulin aspart and insulin glulisine, and weight loss with insulin lispro.[26] In our study, although weight gain was observed in patients who received insulin glulisine, intensification of the RAI regimen did not contribute to a significant increase in BW and BMI while still achieving glycemic control.

The initiation of 1 RAI/day or further intensification may cause hypoglycemia. We did not collect data on events of hypoglycemia in the study patients. At baseline, 32.78% of all RAI users did not receive insulin as a prior medication, and 30.4% of glulisine group did not use insulin as a prior medication in the intensive versus non-intensive group. This would have made a difference in analysing the patients available for final analyses. This number difference occurred because there were patients who did not maintain prior insulin and changed to RAI alone, or there were follow-up losses due to various reasons. In addition, this study could not conclude the pattern of RAI use of other insulin analogs (insulin aspart and insulin lispro) in terms of distribution and analysis as their use was limited to approximately 10% of the enrolled patients and they were not randomized. Since this study focused on the clinical effectiveness of the use of RAI in real-world practice, it did not sufficiently reflect the effect on the glycemic parameters of BI used in combination with RAI. The presence of BI may have affected the reduction of fasting glucose and A1c. Therefore, further studies demonstrating the effect of RAI in the absence of BI on glycemic parameters are needed. Lastly, due to the duration of this study, long-term follow up was not possible to effectively measure the safety and efficacy of comparative intensification therapy of insulin analogs in Korean patients; hence, the results need to be interpreted carefully.

Conclusion

The results from this study will help healthcare providers to understand the real-world clinical practice of combination therapy with RAI analogs, number of daily doses, and the target HbA1c level in Korea from the perspective of appropriate use of RAI analogs. In this study, insulin glulisine was prescribed to the majority of the patients with T2DM Insulin glulisine was the most predominant RAI which significantly improved HbA1c, FPG, and PPG levels up to 6 months. Basal insulin+≥2 RAI injection/day showed better improvement in HbA1c levels and changes in body weight in comparison to basal insulin+1 RAI injection/day. According to the results obtained in the present study, insulin glulisine may prove to be a potential therapeutic choice for management of diabetes.

Abbreviations

AACE, American Association of Clinical Endocrinologists; ADA, American Diabetes Association; ANCOVA, Analysis of covariance; BMI, Body mass index; BW, Body weight; FPG, Fasting plasma glucose; GLP-1 RA, Glucagon-like peptide-1 receptor agonist; HbA1c, Glycated hemoglobin; LOCF, Last observation carried forward; OHAs, Oral hypoglycemic agents; PPG, postprandial plasma glucose; RAIs, Rapid-acting insulins; SAI, Short-acting insulin; T2DM, Type 2 diabetes mellitus; SD, standard deviation.

Data Sharing Statement

Qualified researchers may request access to patient-level data and related documents [including, eg, the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications]. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at https://www.clinicalstudydatarequest.com.

Ethics Approval and Informed Consent

The study protocol was approved by the local institutional review boards and ethics committee.

The study protocol was approved by the local institutional review boards and ethics committee (Supplementary Table 3). The study data were collected after the patients had signed the data release consent form. The study was conducted in accordance with the guiding principles detailed in the 18th World Assembly (Declaration of Helsinki, 1964) and its subsequent amendments, Good Epidemiology Practice guidelines, and national laws and regulations of Korea.

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Author Contributions

Authors HS Kim, KH Lee, and SJ Yoo have made substantial contributions to the conception and design. HS Kim, JM Yu, HC Jang, EK Choi, JH Park, HS Shon, CH Chung, KG Park, JH Cho and SJ Yoo contributed to the acquisition of data. All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article has been submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

Hye Soon Kim, Jae Myung Yu, Hak Chul Jang, Eui Kwang Choi, Jeong Hyun Park, Ho Sang Shon, Choon Hee Chung, Keun-Gyu Park, Jae Hyoung Cho, and Soon Jib Yoo have no conflicts of interest in this work. Won Kim, Kyoung Hwa Lee, and Jee Hyun Lee are employees of Sanofi Aventis Korea.

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