Short Communication
Drug/Regimen

Diabetes Metab J 2022;46:658-662
https://doi.org/10.4093/dmj.2021.0232
pISSN 2233-6079 · eISSN 2233-6087

dmj
DIABETES & METABOLISM JOURNAL

Clinical Efficacy of Sodium-Glucose Cotransporter 2 Inhibitor and Glucagon-Like Peptide-1 Receptor Agonist Combination Therapy in Type 2 Diabetes Mellitus: Real-World Study

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Sodium-glucose cotransporter 2 inhibitor (SGLT2i) and glucagon-like peptide-1 receptor agonist (GLP-1RA) are novel anti-diabetic drugs whose glucose-lowering effect and cardiovascular and renal benefits were evidenced in clinical trials. We investigated the real-world efficacy and safety of the combination of SGLT2i and GLP-1RA in patients with type 2 diabetes mellitus in Korea. The medical records of 104 patients who maintained the combination for at least 1 year were retrospectively reviewed. The change in glycosylated hemoglobin (HbA1c) after 6 months and 1 year of treatment was evaluated. The mean age was 51 years, and 41% were female. The mean baseline HbA1c, body mass index, and duration of diabetes were 9.0%, 28.8 kg/m^2, and 11.7 years, respectively. Compared with baseline, the HbA1c decreased by 1.5% (95% confidence interval [CI], 1.27 to 1.74; $P<0.001$) after 6 months and by 1.4% (95% CI, 1.19 to 1.70; $P<0.001$) after 1 year. Over 1 year, the bodyweight change was −2.8 kg (95% CI, −4.21 to −1.47; $P<0.001$). The combination of SGLT2i and GLP-1RA is effective and tolerable in type 2 diabetes mellitus patients in real-world practice.

Keywords: Diabetes mellitus, type 2; Glucagon-like peptide-1 receptor; Sodium-glucose transporter 2 inhibitors

INTRODUCTION

Sodium-glucose cotransporter 2 inhibitor (SGLT2i) and glucagon-like peptide-1 receptor agonist (GLP-1RA) are novel and effective treatment options for patients with type 2 diabetes mellitus (T2DM) [1]. Both drugs showed cardiovascular benefits and are strongly recommended for T2DM patients with cardiovascular disease (CVD) or at high risk of CVD [2,3]. SGLT2i inhibits renal glucose reabsorption in the proximal tubule, producing glycosuria and ameliorating glucotoxicity [2,3]. GLP-1RA decreases plasma glucose levels by enhancing glucose-stimulated insulin secretion and inhibiting glucagon secretion [2,3]. In clinical trials, the combination of SGLT2i and GLP-1RA was significantly better than either drug alone in glycemic control and weight loss, while having an acceptable safety profile [4-6]. Furthermore, a few retrospective studies reported the effectiveness of this combination [7-9]. The beneficial effects of SGLT2i and GLP-1RA are likely complementary and potentially additive, making them a compelling duet for treating patients with T2DM. However, real-world data regarding this combination therapy in Asian population is lacking. Thus, we investigated the efficacy and safety of GLP-1RA and SGLT2i combination therapy in Korean patients with T2DM in real-world practice.

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Received: Aug. 31, 2021; Accepted: Sep. 19, 2021

METHODS

Study population

We retrospectively reviewed the medical records of 104 T2DM patients at Asan Medical Center (AMC), Korea, who applied the combination of SGLT2i (dapagliflozin or empagliflozin) and GLP-1RA (dulaglutide) for at least 1 year between January 2016 and September 2020. The exclusion process is provided in Supplementary Fig. 1. This study was conducted following the guidelines in the Declaration of Helsinki and was approved by the Institutional Review Board of AMC (2020-1814). Informed consent was waived by the board.

Clinical and laboratory measurements

The baseline data included age, sex, body weight, height, body mass index (BMI), blood pressure (BP), duration of diabetes, use of other medications, and presence of diabetic complications. Laboratory measurements including glycosylated hemoglobin (HbA1c), fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol (LDL-C), liver enzymes, and renal parameters, and adverse events were collected. These data were collected 6 months (±4 weeks) and 1 year (±4 weeks) after initiating the combination therapy.

Dulaglutide was started at 0.75 mg and was escalated to 1.5 mg after 2 to 4 weeks, unless the patients experienced adverse events, reached the glycemic target with 0.75-mg dulaglutide, or desired not to increase the dose.

Outcomes

The study's primary outcome was the efficacy of the combination therapy in glycemic control in 1 year. The secondary outcomes were changes in other laboratory parameters, such as FPG, body weight, BP, lipid parameters, liver enzymes, renal measures, and insulin dose.

Statistical analysis

Continuous variables were expressed as the mean±standard deviation and categorical variables as percentages. Paired *t*-test assessed changes in HbA1c, FPG, and body weight from baseline after 6 months and 1 year. Univariate and multivariate linear regression analyses assessed the parameters affecting the glycemic response. Subgroup analyses compared the reduction of HbA1c according to age, BMI, duration of diabetes, combination sequence, baseline HbA1c, and previous insulin use. All statistical analyses were done using SPSS software version 23.0 for Windows (IBM Co., Armonk, NY, USA).

RESULTS

Baseline characteristics

The baseline characteristics of the study participants are presented in Supplementary Table 1. The mean age was 51.1±10.6 years, and 41.3% were female. The patients were medicated for hypertension and dyslipidemia in 67.3% and 97.1%. Metformin was continued in 98.1% of patients, sulfonylurea in 81.7%, and insulin in 10.6%.

Efficacy of the combination therapy

Changes in the patients' anthropometric and laboratory parameters over 6-month and 1-year periods are shown in Table 1. Changes in HbA1c, FPG, and body weight are shown in Fig. 1. After initiating the combination of SGLT2i and GLP-1RA, HbA1c showed a significant decrease of 1.50% from 9.02%±1.39% at baseline to 7.51%±0.94% at 6 months and 7.57%±0.93% at 1 year ($P<0.001$ for both) (Table 1, Fig. 1A). FPG was also significantly reduced from 177.73±64.61 mg/dL at baseline to 138.21±31.39 mg/dL at 6 months and 137.69±36.34 mg/dL at 1 year ($P<0.001$ for both) (Table 1, Fig. 1B). Body weight showed a decreasing trend after 6 months and was significantly reduced by 2.85 kg after 1 year (from 80.90±15.60 to 78.05±17.20 kg, $P<0.001$) (Table 1, Fig. 1C).

Additionally, the combination therapy significantly reduced systolic blood pressure (SBP) by 3.69 mm Hg ($P=0.015$), TC by 12.19 mg/dL ($P<0.001$), TG by 35.58 mg/dL ($P=0.014$), and LDL-C by 10.49 mg/dL ($P<0.001$), respectively (Table 1). Among the 27 patients on insulin before initiating combination therapy, 16 patients successfully switched from insulin to dulaglutide. In the 11 patients who continued insulin, the total daily insulin dose was significantly reduced from 53.38±24.57 to 45.38±25.80 units per day ($P=0.038$) after 6 months and to 42.54±31.06 units per day ($P=0.024$) after 1 year (Table 1).

Clinical parameters affecting the glucose-lowering effect of the combination therapy

Predicting factors of the glucose-lowering efficacy of 1-year combination therapy were identified as age, baseline HbA1c, baseline FPG through univariate regression analysis (Supplementary Table 2). Multiple linear regression analysis showed that only the baseline HbA1c significantly affected the HbA1c

Table 1. Changes in anthropometric and laboratory parameters at 6-month and 1-year follow-up periods

	Baseline	6-month	*P* value[a]	1-year	*P* value[b]
HbA1c, %	9.02±1.39	7.51±0.94	<0.001	7.57±0.93	<0.001
FPG, mg/dL	177.73±64.61	138.21±31.39	<0.001	137.69±36.34	<0.001
SBP, mm Hg	132.78±16.49	129.13±16.12	0.021	129.09±16.08	0.015
DBP, mm Hg	77.88±11.64	75.47±11.57	0.023	76.04±10.92	0.078
Weight, kg	80.90±15.60	79.95±18.30	0.333	78.05±17.20	<0.001
BMI, kg/m^2	28.78±4.28	28.11±4.40	0.731	27.97±4.35	<0.001
Cr, mg/dL	0.81±0.24	0.83±0.27	0.576	0.83±0.30	0.692
eGFR, mL/min/1.73 m^2	96.87±16.61	95.59±17.47	0.611	95.59±20.45	0.218
AST, IU/L	30.51±15.43	29.58±15.26	0.658	27.94±10.64	0.157
ALT, IU/L	34.93±23.91	31.57±21.52	0.290	31.50±25.52	0.335
TC, mg/dL	143.34±36.53	138.67±35.14	0.132	131.15±26.31	<0.001
TG, mg/dL	223.20±227.56	199.80±215.82	0.118	187.62±176.77	0.014
HDL-C, mg/dL	41.78±10.10	41.61±9.57	0.807	40.82±8.84	0.163
LDL-C, mg/dL	90.46±25.89	84.54±24.89	0.013	79.97±21.35	<0.001
TDI, IU/day	53.38±24.57	45.38±25.80	0.038	42.54±31.06	0.024

Values are presented as mean±standard deviation.
HbA1c, glycosylated hemoglobin; FPG, fasting plasma glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; Cr, creatinine; eGFR, estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TDI, total daily insulin.
[a]Differences in variables from baseline to 6 months, [b]Differences in variables from baseline to 1 year.

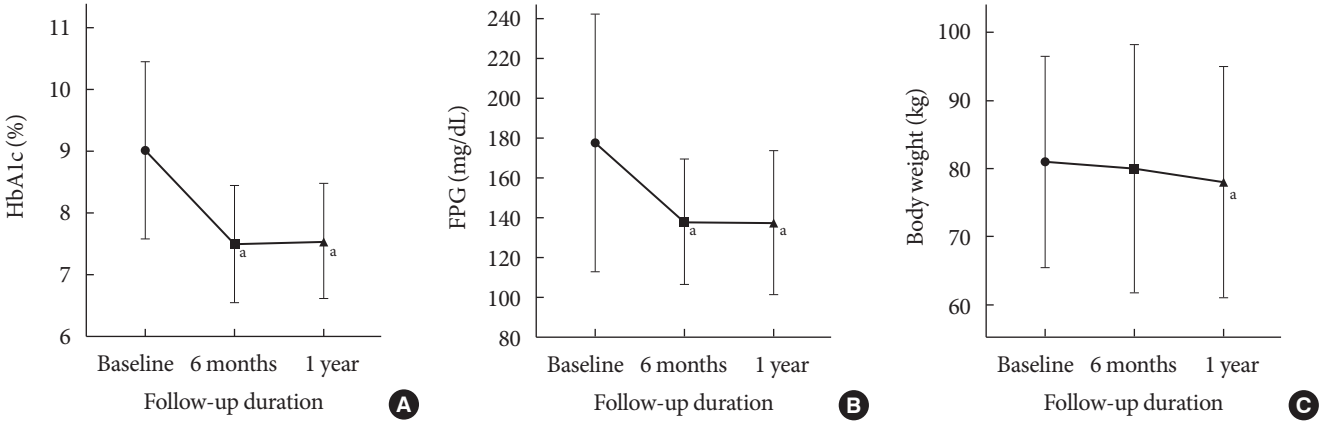

Fig. 1. Efficacy measures. (A) Changes in glycosylated hemoglobin (HbA1c), (B) changes in fasting plasma glucose (FPG), (C) changes in body weight after 6 months and 1 year of combination therapy. Data are presented as mean±standard deviation. [a]$P<0.05$, each compared with baseline.

reduction (Supplementary Table 3).

Subgroup analyses showed that a higher baseline HbA1c level was associated with a significantly greater reduction of HbA1c (Supplementary Fig. 2). HbA1c was decreased by 2.14% in patients with baseline HbA1c >9.0%, compared with 0.79% in patients with HbA1c ≤9.0%. However, there was no significant difference between the subgroups categorized by age, BMI, duration of diabetes, combination sequence, and previous insulin use.

Adverse events

Adverse events were mostly mild (Supplementary Table 4).

Thirteen (12.5%), eight (7.7%), and nine (8.7%) adverse events were reported during 3 months, 6 months, and 1 year of combination treatment, respectively. Gastrointestinal side effects were common at 3-month follow-up, but the incidence decreased as the patients sustained the therapy. Additionally, hypoglycemia, although mild, was reported in five patients at the 1-year follow-up visit.

DISCUSSION

In this real-world data analysis, the combination treatment of SGLT2i and GLP-1RA was effective and safe in patients with T2DM. HbA1c and weight were significantly reduced after 1 year. Additionally, SBP and lipid profile were improved. The baseline HbA1c was associated with the glucose-lowering effect of the combination therapy.

SGLT2i and GLP-1RA emerged as game changers in treating T2DM, as they not only showed efficacy in glycemic control and weight loss but also proved cardiovascular and renal benefits [1]. Hemodynamic changes induced by SGLT2i and anti-atherogenic effects of GLP-1RA are probable mechanisms of cardiovascular benefits [10,11]. Combining the two drugs targeting different pathophysiologic mechanisms of T2DM has been expected to have a synergistic effect [1].

Previous clinical trials showed the effectiveness of the SGLT2i and GLP-1RA combination. In the DURATION-8 trial, patients started the combination of once-weekly exenatide and dapagliflozin, which was significantly better than either drug alone in decreasing HbA1c, weight, and SBP [4]. Additionally, in AWARD-10 and SUSTAIN-9 trials, dulaglutide and semaglutide were superior to placebo when added to SGLT2i in lowering blood glucose and weight [5,6]. The addition of SGLT2 inhibitors to GLP-1RA was also effective and tolerable in clinical trials conducted in Japan [12,13].

Accordingly, a meta-analysis showed that the addition of GLP-1RA to SGLT2i was superior in HbA1c reduction, body weight loss, and lowering of SBP, TC, and LDL-C to SGLT2i alone [14]. Furthermore, a systematic review also showed that the combination reduced HbA1c, body weight, and SBP significantly more than either drug alone [15].

Retrospective studies showed similar results regarding combination therapy. For example, in the study of 79 patients, the combination therapy for 3 to 6 months significantly reduced HbA1c and body weight by 1.05% and 3.07 kg, respectively [8]. Likewise, adding dapagliflozin to GLP-1RA in 109 for a median of 10.9 months resulted in a 0.69% reduction in HbA1c and 2.4 kg reduction in weight [7]. Another Spanish study showed that the combination therapy reduced HbA1c by 1.1% and weight by 3.5 kg weight loss in 212 patients for 16.4±6.5 months [9]. Accordingly, our study showed significant improvement in HbA1c, weight, SBP, and cholesterol levels.

The incidence of adverse events was similar to previous real-world studies [7,9]. However, no genital infection events were recorded, and most of the events were gastrointestinal and injection site problems associated with dulaglutide. The exclusion of fourteen patients who discontinued the combination therapy due to adverse events during the selection process could be the reason for this finding.

The limitations of this study are as follows. First, this study was conducted without a comparison arm. Second, concurrent use of other anti-diabetic, anti-hypertensive, and lipid-lowering agents might have affected the results. Third, because adverse events were only retrospectively reviewed from medical records, missed events might be present. Lastly, only Korean patients from one institution were included in the analysis.

Despite such limitations, to our knowledge, this is the first to analyze the effectiveness of the SGLT2i and GLP-1RA combination in Asian patients in real-world practice. Also, all study patients continued the combination therapy for more than 1 year, longer than most previous studies, providing evidence for long-term efficacy and safety.

In conclusion, SGLT2i and GLP-1RA combination is effective and tolerable in T2DM patients in real-world practice.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2021.0232.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conception or design: W.J.L.
Acquisition, analysis, or interpretation of data: H.S.K., T.Y., C.H.J., J.Y.P., W.J.L.
Drafting the work or revising: H.S.K., T.Y., W.J.L.

Final approval of the manuscript: H.S.K., T.Y., C.H.J., J.Y.P., W.J.L.

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FUNDING

None

ACKNOWLEDGMENTS

None

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