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ORIGINAL RESEARCH

Therapeutic Effects of Switching to Anagliptin from Other DPP-4 Inhibitors in T2DM Patients with Inadequate Glycemic Control: A Non-interventional, Single-Arm, Open-Label, Multicenter Observational Study

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ABSTRACT

Introduction: The effects of switching DPP-4 inhibitors in type 2 diabetes mellitus (T2DM) patients are being widely studied. However, information of which factors affect the therapeutic response is limited. We evaluated the difference in HbA1c lowering effect by comorbidity and other variables after switching to anagliptin in patients with T2DM inadequately controlled by other DPP-4 inhibitors.

Methods: In a multicenter, open-label, single-arm, prospective observational study, patients with T2DM, HbA1c $\geq$ 7.0% who have taken DPP-4 inhibitors other than anagliptin, either alone or in combination (DPP-4 inhibitors + metformin/sulfonylurea (SU)/thiazolidinedione (TZD)/insulin), for at least 8 weeks were enrolled. After the switch to anagliptin, HbA1c and available clinical characteristics were determined.

Results: The change in HbA1c levels from baseline to week 12 and 24 was − 0.40% and − 0.42% in all patients. However, comparing the subgroups without and with comorbidities, the change in HbA1c levels at weeks 12 and 24 was − 0.68% and − 0.89% vs. − 0.27% and 0.22%, respectively. In addition, the proportion of patients achieving HbA1c < 7% from baseline to week 12 and 24 was increased to 70% and 70% vs. 20% and 24%, respectively. Duration of T2DM and different subtype classes of DPP-4 inhibitor did not significantly contribute to the change in HbA1c.

Conclusion: In patients with T2DM poorly controlled by other DPP-4 inhibitors, HbA1c levels were significantly decreased after switching to anagliptin. Given that the change in HbA1c was greater in patients without comorbidities than in patients with comorbidities, switching to anagliptin before adding other oral hypoglycemic agents (OHAs) may be an option in patients without comorbidities.

Keywords: Diabetes mellitus; Type 2; Dipeptidyl peptidase IV inhibitors; Anagliptin; Comorbidities; Switching

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Key Summary Points

Why carry out this study?

Glycemic control depends on the types and doses of hypoglycemic agents, but reports suggest that other factors such as baseline HbA1c, age, duration of T2DM, and comorbidities may also play a role.

Previous switching studies have shown the additional blood glucose control effect, and yet it is still unclear which factors affect the change in glycemic control.

Therefore, we assessed the factors that can predict therapeutic response when switching from previous DPP-4 inhibitors to anagliptin in T2DM patients who had not responded well to other DPP-4 inhibitors.

What was learned from the study?

By switching from other DPP-4 inhibitors to anagliptin, patients without comorbidities had lower HbA1c levels than patients with comorbidities.

This finding suggests that switching to anagliptin may be an option for patients with diabetes mellitus who do not respond to DPP-4 inhibitors and have no comorbidities.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic, progressive disease, and long-term diabetic patients often require multiple combinations of oral hypoglycemic agents (OHAs) since glucose control cannot be managed properly along the duration of the disease [1, 2]. The American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD) and Korean Diabetes Association (KDA) guidelines for T2DM recommend metformin as first-line therapy. However, if the glycemic target is not met with metformin alone, adjunctive treatment with various OHAs is recommended [3, 4].

Dipeptidyl peptidase-4 (DPP-4) inhibitors are suggested as second- or third-line therapy for patients on first-line metformin treatment [3, 4] because of their high efficacy, low risk of hypoglycemia, and neutral effect on body weight [5–11]. In addition, DPP-4 inhibitors have shown greater glucose-lowering efficacy, particularly in Asians. Meta-analysis of many clinical studies has demonstrated that DPP-4 inhibitors are more likely to decrease HbA1c in Asian patients, favoring DPP-4 inhibitors; thus, these drugs are among those most commonly prescribed [12].

Anagliptin is a novel selective DPP-4 inhibitor that improves glycemic control by increasing insulin secretion via incretin stimulation and suppressing excessive glucagon secretion [13]. Because of its short half-life, anagliptin should be taken twice daily [14]. Therefore, it increases GLP-1 levels by more than twofold while decreasing DPP-4 enzymatic activity by > 80% [13]. Several clinical studies have shown that anagliptin has the same blood glucose-lowering effectiveness and safety as other DPP-4 inhibitors. In addition, unlike traditional DPP-4 inhibitors, anagliptin may be effective in patients with high BMI [15, 16].

Glycemic control depends on the types and doses of hypoglycemic agents, but previous reports suggest that other factors such as baseline HbA1c, age, duration of T2DM, and comorbidities may also contribute [17–21]. Considering the addition of DPP-4 inhibitors for blood glucose control, real-world [22] and other studies have reported that switching treatment between DPP-4 inhibitors without additional hypoglycemic agents is also effective [23–28]. Although many switching studies have shown the efficacy of DPP-4 inhibitors, it is still unclear which factor affects the change in therapeutic response. Therefore, this study assessed the therapeutic effects of switching from other DPP-4 inhibitors to anagliptin in T2DM patients with inadequate glycemic control.

METHODS

Participants

The inclusion criteria were as follows: (1) age ≥ 19 years; (2) type 2 diabetes mellitus with a HbA1c ≥ 7.0%; (3) received DPP-4 inhibitors other than anagliptin, either alone or in combination [DPP-4 inhibitors + metformin/sulfonylurea (SU)/thiazolidinedione (TZD)/insulin], for at least 8 weeks. The exclusion criteria were as follows: (1) patients who were given anagliptin before registration; (2) any patient considered ineligible for this study by the investigator. All patients provided informed consent before participating in this study. This study was conducted in compliance with the Declaration of Helsinki and the protocol approved by each institutional or central Institutional Review Board (IRB) including the Catholic University of Korea Bucheon St. Mary's Hospital IRB (no. HC17OODI0113, etc.). The details of ethics committees of participating centers are provided in Supplementary Table S6.

Study Design

This was an open-label, single-arm, multicenter prospective observational study in patients with T2DM. The study was conducted between July 1, 2017, and March 31, 2022 (registered on theClinicalTrials.gov: NCT04267601). Subjects visited the study site at baseline to measure HbA1c and other clinical parameters such as body weight, estimated glomerular filtration rate (eGFR), aspartate aminotransferase (AST), and alanine aminotransferase (ALT). After baseline, data were collected, and the previously taken DPP-4 inhibitors were switched to anagliptin for the following 24 weeks. HbA1c and other clinical parameters were measured in subjects at weeks 12 and 24. Baseline concomitant antidiabetic regimens (such as metformin, TZD, insulin, SU, and others) were maintained throughout the study.

The main objective of this study was to evaluate therapeutic responses in T2DM patients after switching from other DPP-4 inhibitors to anagliptin. The primary endpoint was to investigate the change in HbA1c according to switching among DPP-4 inhibitors.

Subgroup Analysis

Overall, 1119 patients with HbA1c ≥ 7% were analyzed by DPP-4 binding pattern, maximum serum concentration (Cmax) of DPP-4 inhibitors, comorbidities, and T2DM duration subgroups to evaluate the factors influencing therapeutic response (Fig. 1); 223 patients had partially missing data and therefore were eliminated.

DPP-4 has a wide substrate binding pocket composed of four subsites (S1, S1′, S2, S2′, and S2 extensive), and current inhibitors bind to DPP-4 by fitting into multiple subsites. In particular, Class I inhibitors (saxagliptin and vildagliptin) bind to the S1 and S2 subsites, the core of the binding and central scaffolds of all Class I, II, and III inhibitors. Class II inhibitors (alogliptin and linagliptin) bind to S1, S2, S1′, and S2′ pockets. Lastly, Class III inhibitors (anagliptin, evogliptin, gemigliptin, sitagliptin, teneligliptin) bind to S1, S2, and S2 extensive pockets [29]. To determine the association between pharmacokinetic and pharmacodynamic parameters, correlation analysis was conducted between changes of HbA1c according to switching from DPP-4 inhibitors to anagliptin and Cmax of each DPP-4 inhibitor.

Comorbidities among patients in this study include the following types: dyslipidemia, hypertension, angina, diabetic retinopathy, and atherosclerosis. Only ≥ 5% reported comorbidities among the study patients were analyzed. When categorized by comorbidities, there were 322 patients without comorbidities and 797 with comorbidities.

The duration of T2DM was then classified into < 5 years, 5–10 years, and < 10 years (Supplementary Figure S1). When the duration of T2DM was further classified into each group, there were 153 patients with < 5-year duration of T2DM, 51 patients with 5–10-year duration of T2DM, and 31 patients with ≥ 10-year duration of T2DM among patients without comorbidities and 128 patients with < 5-year duration of T2DM, 178 patients with 5–10-year duration

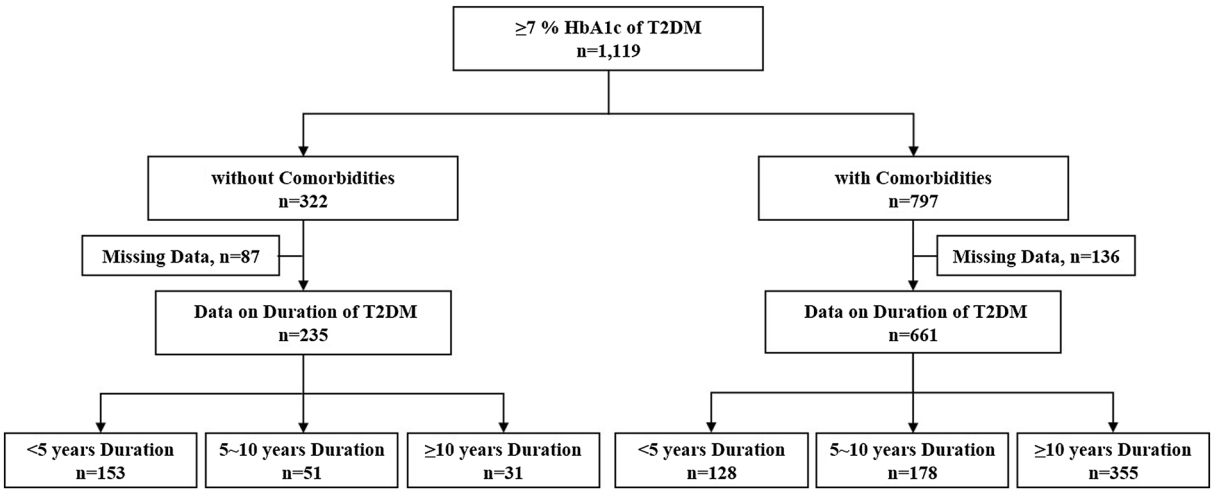


Fig. 1 Flowchart for the subgroup analysis

of T2DM, and 355 patients with ≥ 10-year duration of T2DM among patients with comorbidities.

Statistical Analysis

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Continuous variables were described using descriptive statistics [mean ± standard deviation (SD)], and categorical variables were presented as counts (percentages). A p value < 0.05 was considered statistically significant.

RESULTS

Patient Disposition and Demographics

Table 1 shows the baseline characteristics of 1119 patients with T2DM showing HbA1c ≥ 7% despite treatment with DPP-4 inhibitors. The DPP-4 inhibitors in the previous therapy, including saxagliptin, vildagliptin, alogliptin, linagliptin, evogliptin, gemigliptin, sitagliptin, and teneligliptin, were switched to anagliptin. Then, using comorbidities such as dyslipidemia, hypertension, angina, diabetic retinopathy, and atherosclerosis as subgroup classification, the baseline characteristics that showed a significant difference between the without comorbidities group and the with comorbidities group were the duration of T2DM (4.0 vs. 11.4 years, $p < 0.001$) and the frequency of concomitant medications. The proportion of patients using concomitant medications was higher in the with comorbidities group.

Efficacy

The overall change in HbA1c was − 0.40% at week 12 and − 0.42% at week 24, indicating a significant reduction from baseline ($p < 0.05$) (Fig. 2, Supplementary Table S1). We analyzed HbA1c decreasing effect in patients with baseline HbA1c values based on 8%, and both groups with baseline HbA1c of < 8 and ≥ 8% showed significant reduction. These were greater in patients with baseline HbA1c ≥ 8% (− 0.69% at week 12, − 0.73% at week 24) compared to < 8% (− 0.24% at week 12, − 0.24% at week 24) (Supplementary Table S2). We also evaluated the change in HbA1c after switching to anagliptin from other DPP-4 inhibitors according to DPP-4 binding patterns (Class I, II, III) (Fig. 2), and there were no differences in HbA1c reduction between binding patterns (Fig. 2, Supplementary Table S1). Nonetheless, the correlation analysis between the change in HbA1c and the maximum serum concentration (Cmax) of DPP-4 inhibitors in all groups suggests a greater reduction in HbA1c

Table 1 Baseline characteristics of study population

	Without comorbidities		With comorbidities		*p* value
	n	Mean ± SD or *n* (%)	*n*	Mean ± SD or *n* (%)	
Sex, male	322	191 (59%)	797	461 (58%)	0.651
Age (years)	322	63.0 ± 12.1	797	64.1 ± 10.6	0.153
Duration of T2DM (years)	235	4.0 ± 5.0	661	11.4 ± 7.3	< 0.001
HbA1c (%)	322	7.89 ± 0.94	797	7.97 ± 0.88	0.141
Body weight (kg)	92	66.7 ± 13.2	535	67.2 ± 11.2	0.728
eGFR (ml/min)	76	98.1 ± 93.9	569	84.2 ± 26.4	0.204
AST (U/l)	77	25.1 ± 10.4	581	27.8 ± 17.9	0.055
ALT (U/l)	77	26.5 ± 14.0	581	29.5 ± 21.1	0.100
Concomitant medications, *n* (%)					
Metformin	322	124 (39%)	797	712 (89%)	< 0.001
Thiazolidinedione (TZD)	322	3 (1%)	797	70 (9%)	< 0.001
Insulin	322	1 (0.3%)	797	81 (10%)	< 0.001
Sulfonylurea (SU)	322	17 (5%)	797	412 (52%)	< 0.001
Other	322	0 (0%)	797	34 (4%)	< 0.001
Prior DPP-4 inhibitor therapies, *n* (%)					
Saxagliptin	322	12 (4%)	797	44 (6%)	0.213
Vildagliptin	322	36 (11%)	797	100 (13%)	0.526
Alogliptin	322	56 (17%)	797	76 (10%)	< 0.001
Linagliptin	322	73 (23%)	797	151 (19%)	0.157
Evogliptin	322	11 (3%)	797	14 (2%)	0.089
Gemigliptin	322	18 (6%)	797	82 (10%)	0.013
Sitagliptin	322	88 (27%)	797	235 (29%)	0.471
Teneligliptin	322	28 (9%)	797	95 (12%)	0.119
Comorbidities (> 5%), *n* (%)					
Dyslipidemia	–		797	591 (74%)	
Hypertension	–		797	525 (66%)	
Angina	–		797	113 (17%)	
Diabetic retinopathy	–		797	73 (9%)	
Atherosclerosis	–		797	70 (9%)	

eGFR estimated glomerular filtration rate; *AST* aspartate aminotransferase; *AST* alanine aminotransferas

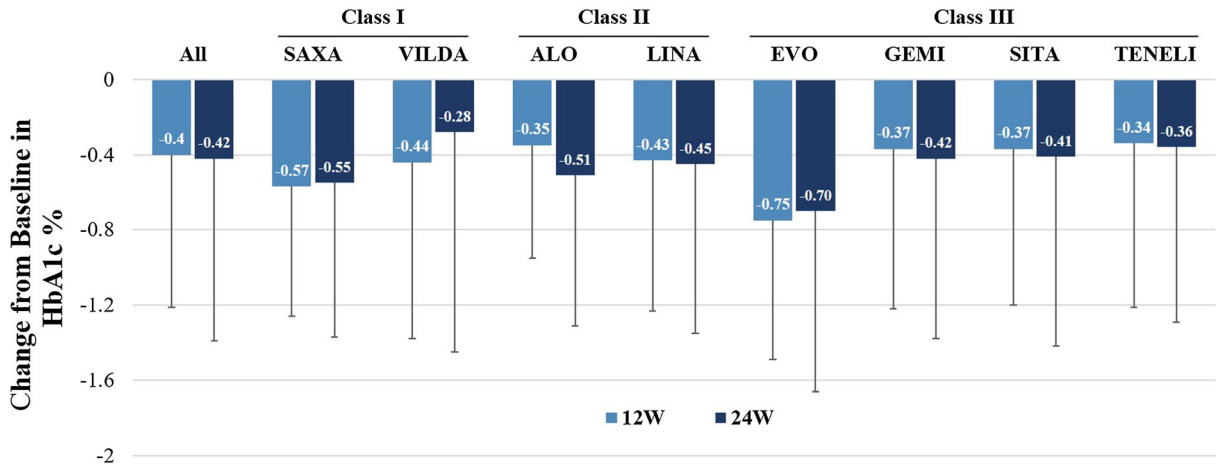


Fig. 2 Change from baseline in HbA1c according to switching from DPP-4 inhibitors to anagliptin in T2DM patients. *SAXA* saxagliptin; *VILDA* vildagliptin; *ALO* alogliptin; *LINA* linagliptin; *EVO* evogliptin; *GEMI* gemigliptin; *SITA* sitagliptin; *TENELI* teneligliptin; *12w* 12 weeks; *24w* 24 weeks

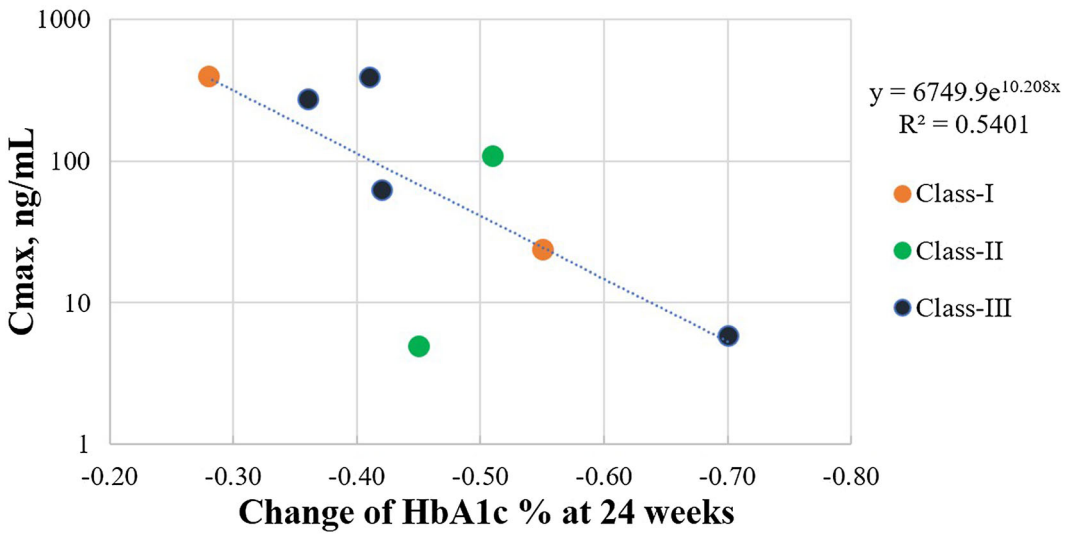
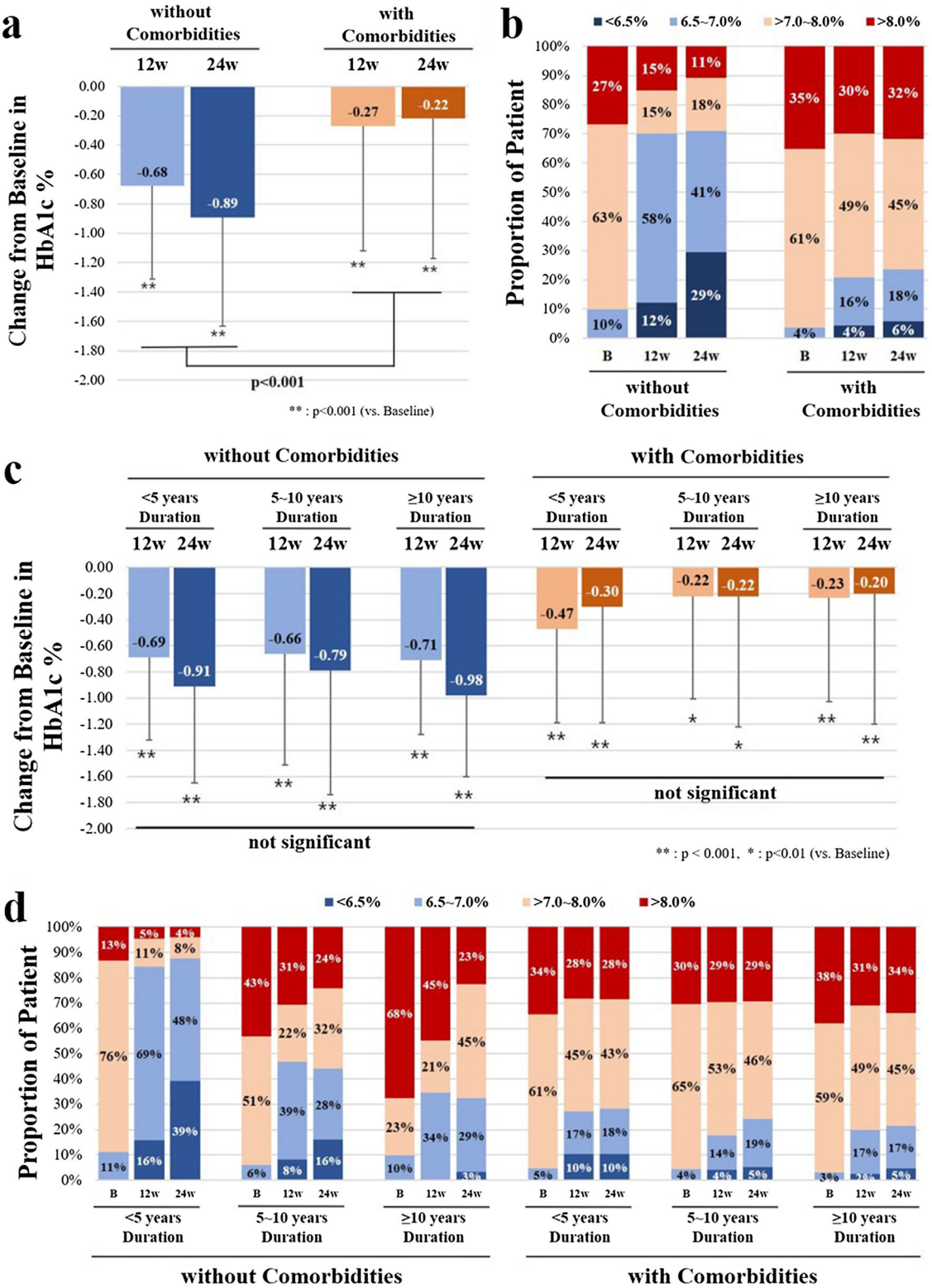


Fig. 3 Relation between change from baseline in HbA1c according to switching from DPP-4 inhibitors to anagliptin and maximum serum concentration (C_{max}) of DPP-4 inhibitors

when the DPP-4 inhibitors with low Cmax were switched to anagliptin ($r^2 = 0.5401$) (Fig. 3, Supplementary Table S1) [30].

In a further analysis by comorbidities, the change of HbA1c in the without comorbidities group was − 0.68% at week 12 and − 0.89% at week 24, showing a significant reduction from baseline ($p < 0.001$). In comparison, the change of HbA1c in the with comorbidities group was − 0.27% at week 12 and − 0.22% at week 24, showing a significant but less pronounced reduction from baseline ($p < 0.05$) than in the without comorbidities group (Fig. 4-a, Supplementary Table S3).

In the without comorbidities group, the proportion of patients who achieved the HbA1c target of < 7% was 10% at baseline, 70% (including 12% below 6.5% and 58% between 6.5 and 7%) at week 12, and 70% (including 29% below 6.5% and 41% between 6.5 and 7%) at


a
without Comorbidities
with Comorbidities
12w 24w 12w 24w
Change from Baseline in HbA1c %
0.00 -0.20 -0.40 -0.60 -0.80 -1.00 -1.20 -1.40 -1.60 -1.80 -2.00
-0.68 -0.89 -0.27 -0.22
**
p<0.001
** : p<0.001 (vs. Baseline)
b
<6.5% 6.5~7.0% >7.0~8.0% >8.0%
Proportion of Patient
100% 90% 80% 70% 60% 50% 40% 30% 20% 10% 0%
27% 63% 10%
15% 58% 12%
11% 18% 41% 29%
35% 61% 4%
30% 49% 16% 4%
32% 45% 18% 6%
B 12w 24w B 12w 24w
without Comorbidities
with Comorbidities
c
without Comorbidities
with Comorbidities
<5 years Duration
5~10 years Duration
≥10 years Duration
12w 24w
Change from Baseline in HbA1c %
0.00 -0.20 -0.40 -0.60 -0.80 -1.00 -1.20 -1.40 -1.60 -1.80 -2.00
-0.69 -0.91 -0.66 -0.79 -0.71 -0.98 -0.47 -0.30 -0.22 -0.22 -0.23 -0.20
not significant
not significant
** : p < 0.001, * : p<0.01 (vs. Baseline)
d
<6.5% 6.5~7.0% >7.0~8.0% >8.0%
Proportion of Patient
100% 90% 80% 70% 60% 50% 40% 30% 20% 10% 0%
13% 76% 11%
5% 11% 16%
4% 8% 48% 39%
43% 51% 6%
31% 22% 39% 8%
24% 32% 28% 16%
68% 23% 10%
45% 21% 34%
23% 45% 29% 3%
34% 61% 5%
28% 45% 17% 10%
28% 43% 18% 10%
30% 65% 4%
29% 53% 14% 4%
29% 46% 19% 5%
38% 59% 3%
31% 49% 17% 2%
34% 45% 17% 5%
B 12w 24w
<5 years Duration
5~10 years Duration
≥10 years Duration
without Comorbidities
with Comorbidities

◀**Fig. 4** Impact according to switching from dipeptidyl peptidase-4 inhibitors to anagliptin in T2DM patients. **a** Change from baseline in HbA1c by comorbidities. **b** Proportion of HbA1c target achieved by comorbidities. **c** Change from baseline in HbA1c by duration of T2DM. **d** Proportion of HbA1c target achieved by duration of T2DM. *B* baseline; *12w* 12 weeks; *24w* 24 weeks

week 24. The fraction of patients with < 6.5% HbA1c after switching to anagliptin increased throughout treatment. Contrastingly, in the with comorbidities group, the proportion was 4% at baseline, 20% (4% < 6.5% and 16% between 6.5 and 7%) at week 12, and 24% (6% < 6.5% and 18% between 6.5 and 7%) at week 24 (Fig. 4b, Supplementary Table S4).

We evaluated the change in HbA1c after switching to anagliptin according to the duration of T2DM (Fig. 4c). In the without comorbidities group, there was no difference in HbA1c change by the duration of T2DM: − 0.69% at week 12 and − 0.91% at week 24 in patients with < 5-year duration, − 0.66% at week 12 and − 0.79% at week 24 in the patients with 5–10-year duration, and − 0.71% at week 12 and − 0.98% at week 24 in the patients with ≥ 10-year duration ($p > 0.05$) (Fig. 4c, left; Supplementary Table S3). Similarly, there was no difference in the changes in HbA1c by the duration of T2DM in the with comorbidities group: − 0.47% at week 12 and − 0.30% at week 24 in patients with < 5-year duration, − 0.22% at week 12 and − 0.22% at week 24 in the patients with 5–10-year duration, and − 0.23% at week 12 and − 0.20% at week 24 in the patients with ≥ 10-year duration ($p > 0.05$) (Fig. 4c, right; Supplementary Table S3). Regardless of the duration of T2DM, the changes in HbA1c in the without comorbidities group were significantly more than those observed in the with comorbidities group.

The proportion of patients who achieved the HbA1c target of < 7% in the without comorbidities group was 11% at baseline, 85% at week 12, and 87% at week 24 with < 5-year duration of T2DM; in patients with 5–10-year duration, the proportion was 6% at baseline, 47% at week 12, and 44% at week 24; in patients with ≥ 10-year duration, the proportion was 10% at baseline, 34% at week 12, and 32% at week 24 (Fig. 4d, left; Supplementary Table S4). In the with comorbidities group, the proportion of patients who achieved the HbA1c target of < 7% was 5% at baseline, 27% at week 12, and 28% at week 24 with < 5-year duration of T2DM; in patients with 5–10-year duration, the proportion was 4% at baseline, 18% at week 12, and 24% at week 24; in patients with ≥ 10 years of duration, the proportion was 3% at baseline, 19% at week 12, and 22% at week 24 (Fig. 4d, right; Supplementary Table S4). The multivariate analysis was conducted using ANCOVA with concomitant medication, type of therapy before switching, duration of diabetes, and class of DPP-4 inhibitors as covariates. The change of HbA1c was significant between with and without comorbidities at week 24 (Supplementary Table S5).

Clinical Characteristics

Table 2 demonstrates the clinical characteristics of the study subjects with and without comorbidities after switching from DPP-4 inhibitors to anagliptin. Body weight, eGFR, and AST values did not change after switching to anagliptin ($p > 0.05$) at weeks 12 and 24. These results were unchanged when analyzed by comorbidity and duration of T2DM. However, ALT decreased significantly from 29.2 U/l at baseline to 26.8 U/l at week 12 ($p = 0.021$); ALT decreased to 27.5 U/l at week 24, but not significantly ($p > 0.05$).

Discussion

Current treatment for patients with T2DM who do not achieve adequate glucose control recommends adding various OHAs to previous therapy [3, 4]. Metformin is prescribed as first-line anti-diabetic treatment, and if the patients who taking metformin with OHA has insufficient glycemic control, dose increase or addition of other agent is required. However, this strategy may result in increased financial burdens and safety risks. In practice, switching to a different DPP-4 inhibitor improves glycemic control rather than a step-up approach to DPP-4

Table 2 Clinical characteristics of study groups according to switching from DPP-4 inhibitors to anagliptin in T2DM patients with and without comorbidities

	Total			Without comorbidities			With comorbidities		
	n	Mean ± SD	*p* value	*n*	Mean ± SD	*p* value	*n*	Mean ± SD	*p* value
Hemoglobin A1c (HbA1c, %)									
Baseline	1119	7.95 ± 0.90	–	235	7.84 ± 0.91	–	661	7.99 ± 0.84	–
12 weeks	952	7.55 ± 0.91	< 0.001	231	7.15 ± 0.86	< 0.001	540	7.73 ± 0.90	< 0.001
24 weeks	1108	7.53 ± 1.04	< 0.001	234	6.95 ± 0.82	< 0.001	654	7.76 ± 1.02	< 0.001
Body weight (kg)									
Baseline	627	67.1 ± 11.5	–	73	66.7 ± 13.7	–	516	67.2 ± 11.1	–
12 weeks	404	66.5 ± 11.2	0.103	38	65.4 ± 14.2	0.064	354	66.7 ± 10.7	0.096
24 weeks	357	66.9 ± 10.9	0.428	38	66.1 ± 13.4	0.219	310	67.2 ± 10.5	0.483
Estimated glomerular filtration rate (eGFR, ml/min)									
Baseline	645	85.9 ± 40.8	–	60	102.6 ± 104.1	–	522	84.5 ± 27.0	–
12 weeks	510	84.6 ± 34.5	0.804	48	86.5 ± 24.4	0.506	419	83.3 ± 26.7	0.345
24 weeks	554	83.9 ± 27.5	0.165	49	88.9 ± 33.9	0.758	462	84.1 ± 27.4	0.476
Aspartate aminotransferase (AST, U/l)									
Baseline	658	27.4 ± 17.2	–	61	25.6 ± 10.6	–	532	27.1 ± 15.5	–
12 weeks	515	26.1 ± 13.2	0.091	46	24.6 ± 11.7	0.980	424	26.2 ± 13.4	0.455
24 weeks	562	25.7 ± 14.4	0.069	49	24.0 ± 9.8	0.301	468	26.1 ± 15.2	0.184
Alanine aminotransferase (ALT, U/l)									
Baseline	658	29.2 ± 20.4	–	61	27.4 ± 14.6	–	532	28.8 ± 18.9	–
12 weeks	515	26.8 ± 16.0	0.021	46	25.9 ± 16.2	0.518	424	27.1 ± 16.4	0.320
24 weeks	562	27.5 ± 20.0	0.192	49	25.6 ± 15.5	0.128	468	27.9 ± 21.0	0.086

inhibitor-containing regimens. Many previous studies have investigated the additional glucose-lowering effect of switching DPP-4 inhibitors and reported a significant reduction in HbA1C after switching [23–28]. As a result, switching therapy has emerged as a viable treatment option for effectively lowering HbA1c in diabetic patients. Therefore, finding a factor

that can predict therapeutic response when changing drugs between DPP-4 inhibitors is critical.

In our study, the patients who switched from other DPP-4 inhibitors to anagliptin had a change in HbA1c level of − 0.42% at week 24. Previous studies showed that DPP-4 inhibitors switching to teneligliptin resulted in changes of − 0.39% (12w), − 0.44% (24w), and − 0.52% (52w) [24]. Also, switching from sitagliptin 50 mg to vildagliptin 100 mg resulted in a reduction of HbA1c from 8.15% to 7.86% after 6 months. In this study, the reduction of HbA1c was comparable to glucosidase (GI) type add-on therapy (acarbose, voglibose, or miglitol) and was even more effective than increasing the DPP-4 inhibitor dosage [25]. All these results suggest that switching between DPP-4 inhibitors may be beneficial.

To identify a factor that can predict therapeutic response when switching anagliptin from other DPP-4 inhibitors, we first assessed the efficacy of lowering HbA1c by subgroups. In our study, having no comorbidities was a predicted therapeutic factor for improved glucose control with switching therapy. The change in HbA1c in patients without comorbidities was − 0.89% at week 24, whereas it was − 0.22% at week 24 in the with comorbidities group. Also, in the without comorbidities group, the proportion of reaching the target of < 6.5% HbA1c after switching was much more significant than those in the with comorbidities group. The clinical implication of HbA1c < 6.5% indicates that the patient is in the prediabetes range, indicating that the risk of diabetic complications is lower [31, 32]. Although the reduction in HbA1c following switching to anagliptin was more significant in patients with baseline HbA1c ≥ 8%, baseline HbA1c was similar in the group with (7.97%) and without comorbidities (7.89%), so more decreasing efficacy without comorbidities is still meaningful (Table 2, Supplementary Table S2). Consequently, our findings suggest that switching to anagliptin may be an option for type 2 diabetic patients who exhibit an inadequate response to DPP-4 inhibitors and have no comorbidities.

Since it is known that the duration of diabetes is an independent factor impacting HbA1c control, we examined the effect of T2DM duration on HbA1c change [33, 34]. There was no difference in the reducing effect of HbA1c based on the duration of T2DM in the groups without and with comorbidities. However, we observed that switching to anagliptin early in treatment will be most effective in the without comorbidities group because the proportion reaching the target HbA1c of < 7% was highest in the < 5-year duration T2DM patients (Fig. 4-d, Supplementary Table S4).

DPP-4 inhibitors interact differently with the active sites of DPP-4 and are thus divided into three classes, with anagliptin belonging to Class III (binds to S1, S2, S1′, and S2 extensive subsites) [35, 36]. In our study, we evaluated the effect of switching from class I, II, or III to anagliptin by classifying the DPP-4 inhibitors used before switching to anagliptin based on their binding characteristics and observed no difference in HbA1c change.

To further explain the additional HbA1c-lowering effect after switching to anagliptin, we examined the correlation between the maximum serum concentration (Cmax) of DPP inhibitors (r^2 = 0.5401). Switching from DPP-4 inhibitors with a lower Cmax to anagliptin (Cmax, 476 ng/ml) resulted in a more significant reduction in HbA1c. Considering these findings, DPP-4 inhibitors with a low Cmax are unlikely to inhibit existing or newly produced DPP-4 target proteins entirely. Reports indicate that all DPP-4 inhibitors can antagonize > 80% of DPP-4 [37, 38], but the Cmax of the drug for each target organ may vary depending on the DPP-4 inhibitor. The evidence that Cmax affects the therapeutic response is unclear. The Cmax value is likely to vary depending on the characteristics of the patients involved in the study (especially by ethnicity). However, according to Erina Shigematsu et al. [28], the switch from vildagliptin (50 mg, twice daily; Cmax 397 ng/ml) to sitagliptin (100 mg, daily; Cmax 390 ng/ml) resulted in no change in HbA1c, but the switch from alogliptin (25 mg, twice daily; Cmax 110 ng/ml) to sitagliptin (100 mg, daily; Cmax 390 ng/ml) produced a significant reduction in HbA1c (− 0.3%, $p < 0.05$).

This study has several limitations. First, because it was a non-comparative, single-arm

study without a control group, some confounding factors, such as concomitant diseases or other heterogeneous drugs, might have influenced glycemic control. Additionally, the possibility of confounding factors and bias due to the limited number of patients in the subgroups cannot be ruled out. Further mechanism analysis such as functional assay of α- and β-cells is needed to understand the factors influencing glycemic control, and these will provide the exact scientific evidence. Second, it is unclear whether the characteristics of the patient group that can benefit from switching to anagliptin are specific to anagliptin, which warrants further studies. Third, there is the risk of inaccuracy in the presence of comorbidities since it relies only on the patient's record rather than the actual results of a medical examination. Consequently, an additional randomized-controlled trial with cross-over design between anagliptin and other DPP-4 inhibitors is required to confirm the switching effect in the future.

In conclusion, this was the first study to evaluate the effect of comorbidities and duration of T2DM on HbA1c reduction after switching between DPP-4 inhibitors. Our findings will help identify patients who would benefit from switching with an additional HbA1c-lowering effect.

CONCLUSION

In patients with T2DM poorly controlled by other DPP-4 inhibitors, HbA1c levels were significantly decreased after switching to anagliptin. Because the change in HbA1c was greater in patients without comorbidities than in those with comorbidities, switching to anagliptin before adding additional OHAs may be an option in patients without comorbidities. By switching between DPP-4 inhibitors, more benefits can be expected, such as lower healthcare costs, better patient compliance, and improved safety.

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Compliance with Ethics Guidelines. This study was performed in compliance with the Korea Good Clinical Practice (KGCP), International Council for Harmonization-GCP (ICH-GCP), and all applicable regulations. This study was reviewed and approved by the respective Institutional Review Boards (IRB) and details of ethics committees are provided in Supplementary Table S6. All patients provided informed consent before participating in this study. This study was conducted in compliance with the Declaration of Helsinki.

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

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