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Original

Long Term Evaluation of Glycemic Control in Patients with Type 2 Diabetes Receiving Either Alogliptin and Lansoprazole or Alogliptin Mono-therapy for 3 Months Followed by Alogliptin Mono-therapy : A Retrospective Analysis

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Conflict of interest : The authors have declared that they have no conflicts of interest.

SUMMARY

Aims : This study was the retrospective analysis of the previous study named as APPLE study (study of combination effect of AlogliPtin and lansoPrazoLE on glycemic control in patients with type 2 diabetes), in which the effect of the combination therapy of alogliptin (a dipeptidyl peptidase-4 inhibitor, DPP4-I) and lansoprazole (a proton pump inhibitor, PPI) was compared with alogliptin mono-therapy without PPI on glycemic control in a randomized open-label study design. The aim of this study was to investigate whether "so called" legacy effect of proton pump inhibitor on glycemic control is observed.

Patients and Methods : In the patients that participated in the APPLE study (3 months observation ; total : 100 patients), the patients who continued the intake of alogliptin at least more than 1 year after the registration (enrollment) in APPLE study was evaluated on glycemic control retrospectively. As a rule, the administration of lansoprazole in combination group was discontinued after the finish of 3 months- of the APPLE study. Twenty-six patients in the alogliptin mono-therapy group and 26 patients in combination group met the requirement in this analysis. Mean observation periods were respectively 16 months. In these patients, the number of patients in whom all diabetic drugs were not changed in observation-period was respectively 18 in alogliptin mono-therapy group and 17 in combination group.

Results : The decrease of HbA1c was maintained also after long term observation (16 months) in both alogliptin mono-therapy and combination groups (the decrease was respectively -1.054 ± 0.548 and $-1.123 \pm 0.723\%$), which was similar compared with that observed in 3 months-APPLE study. There were no significant differences in change of HbA1c and fasting plasma glucose (FPG) at the time in enrollment of APPLE study and at final visit (approximately 16 weeks) between these groups. The significant difference in change of HbA1c and FPG was not found also between alogliptin mono-therapy and combination group in the subgroup of patients where all diabetic drugs were unchanged during observation period.

Conclusion : This study found that the legacy effect of PPI on glycemic control was not apparent more than 9 months after the APPLE study. Based on the results in the previous APPLE study and in this current retrospective study, we concluded that the add-on effect of PPI for DPP4-I on glycemic control in patients with type 2 diabetes is not clinically apparent.

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Key Words : gastrin, PPI, DPP4-I, type 2 diabetes

INTRODUCTION

Gastrin is a peptide hormone produced mainly in the G cells of the pyloric antrum of the stomach [1,2]. The main role of gastrin is the promotion of gastric acid secretion from the parietal cells of the stomach. Gastrin can also act as a growth factor and stimulate gastric cell proliferation[3,4]. In an animal model in which pancreatic tissue remodeling is promoted, it is reported that gastrin increases β cell neogenesis in the pancreatic ductal complex[5,6]. Although the effect of gastrin on adult β cell neogenesis appears to be observed only during pancreatic tissue remodeling[5,7], interestingly, in combination with other hormones, such as glucagon-like peptide-1 (GLP-1), gastrin becomes to be able to enhance β cell neogenesis in ductal cells, even when this agent is added in animal models, such as *db/db* mice (a model of type 2 diabetes) and non-obese diabetic (NOD) mice (a model of type 1 diabetes)[8,9]. In these models, pancreatic remodeling is not necessarily occurring. Although gastrin cannot be administrated orally, oral proton pump inhibitors (PPIs), which are widely used clinically for the treatment of gastro-esophageal reflex disease, gastritis due to excess stomach acid, and gastric ulcers[10], indirectly elevate serum gastrin levels[11~16]. It is also reported that, in NOD mice, the combination therapy of a PPI with a dipeptidyl peptidase-4 inhibitor (DPP4-I), which blocks degradation of GLP-1 by DPP4 resulting in the elevation of serum active GLP-1 levels, was more effective on glycemic control than that of each drug used in monotherapy[17]. Furthermore, a recent study showed that combination therapy with exendin-4 (a GLP-1 receptor agonist) and omeprazole (a PPI) more effectively improved glycemic control over that of each drug used separately in *db/db* mice[18]. These results suggest the possibility that combination therapy, including a PPI and a GLP-1 receptor agonist (or a DPP4-I), may be more effective for inhibition of progression in both type 1 and type 2 diabetes, and may more effectively improve glycemic control, compared with that in those patients using a PPI or GLP-1 receptor agonist (or DPP4-I) as mono-therapy. Although many clinical studies demonstrate that PPIs improved glycemic control in patients with type 2 diabetes[19~25] with some in disagreement[26,27], there are no reports investigating the effect of a combination therapy of a DPP4-I and a PPI in these patients (for review see reference[28]. Based on these backgrounds, we recently investigated the effect of a combination therapy of alogliptin (a DPP4-I) and lansoprazole (a PPI) compared with alogliptin mono-therapy on glycemic control in patients with type 2 diabetes in a randomized open-label study named as APPLE (study of combination effect of AlogliPtin and lansoPrazoLE on glycemic control in patients with type 2 diabetes)[29]. Contrary to our expectation, the effect of the combination therapy on glycemic control was equal to that of alogliptin mono-therapy during a 3-month study period. However, if the expected effect of this combination therapy on glycemic control is based partially on the increased β cell mass by neogenesis in ductal cells, the effect on glycemic control might be observable only after a relatively long term ; i.e., "so called" legacy effect. Therefore, we performed a retrospective analysis on the patients in the APPLE study after its completion. At the end of the 3-month APPLE study, the patients in combination therapy with alogliptin and lansoprazole discontinued the lansoprazole as a rule. In the patients who were enrolled in APPLE study and who continued taking alogliptin, the glycemic control was evaluated more than 9 months after the finish of the study.

PATIENTS and METHODS

This study was the retrospective analysis of the our previous study named as APPLE study. In the APPLE study, the effect of the combination therapy of alogliptin and lansoprazole compared with alogliptin mono-therapy without PPI on glycemic control was prospectively evaluated in a randomized open-label study design. All subjects gave informed consent for inclusion in the APPLE study. The APPLE study was approved by the Local Ethics Committee in Dokkyo Medical University Koshigaya Hospital and was performed according to the guidelines of the Declaration of Helsinki. APPLE study has been registered at UMIN 0000009445. For the details on the APPLE study, see reference[29]. This retrospective analysis of APPLE study was approved by the Bioethics Committee in Dokkyo Medical University Koshigaya Hospital (Approval number : Koshigaya-27002)

In the patients that participated in APPLE study (to-

Table 1 Clinical features at baseline in alogliptin and alogliptin with lansoprazole groups

	Alogliptin	Alogliptin + lansoprazole	P values
No. (male/female)	26 (13/13)	26 (13/13)	—
Age (year)	66.9 ± 8.9	64.4 ± 8.4	0.3021
BMI (kg/m^2)	23.7 ± 3.5	24.8 ± 3.6	0.2842
FPG (mg/dL)	162.7 ± 37.7	164.2 ± 38.6	0.8850
HbA1c (%)	7.8 ± 0.6	7.8 ± 0.6	0.7299
Diabetic Therapy			
SU S1/S2/S3	4/11/5	8/8/2	
Metformin	2	2	
AGI	1	3	
Pioglitazone	0	1	
None	3	2	

BMI : body mass index, FPG : fasting plasma glucose, HbA1c : hemoglobin A1c, SU : sulfonylurea, AGI : alfa-glucosidase inhibitor

Data are expressed as mean ± SD. P : p value, S1 : SU alone, S2 : SU and/or metformin, pioglitazone, AGI. S3 : SU, and/or pioglitazone, AGI,

tal : 100 patients), the patients who continued the intake of alogliptin at least more than 1 year after the registration (enrollment) in the APPLE study were evaluated on glycemic control retrospectively. Twenty-six patients in combination group and 26 patients in alogliptin mono-therapy group met the inclusion requirements. The number of patients in whom sulfonylurea (SU) was reduced after the finish of the APPLE study was 6 in alogliptin mono-therapy group and 5 in combination group. Mean observation periods were 16 months in both groups. The clinical features at baseline of the patients in both alogliptin mono-therapy group and combination group who met the requirements are summarized in Table 1. There were no significant differences in age, BMI, FPG, HbA1c between these groups. The number of patients in whom all diabetic drugs were not changed during observation-period was 18 in alogliptin mono-therapy group and 17 in combination group. In the combination group, although, as a rule, the patients discontinued the intake of lansoprazole at the time point of the finish of APPLE study as previously described, 3 patients continued taking lansoprazole at their request. These patients had had mild gastrointestinal symptoms before enrollment of the APPLE study, and after taking lansoprazole these symptoms improved.

Statistical methods. The two time points for each parameter for an individual were compared using a paired t-test. Comparisons between the two groups were made using an unpaired t-test for normally distributed data (confirmed by a χ^2 test) ; a Student t-test or a Welch t-test was chosen based on the homogeneity of variance calculated by an F-test. Comparisons of hemoglobin A1c (HbA1c) and fasting plasma glucose (FPG) in alogliptin- and those in alogloptin with lansoprazole-treated patients for changes from baseline were assessed using an analysis of variance (ANCOVA) model with treatment as fixed effects and the corresponding baseline value as a covariate. For HbA1c and FPG, least square (LS) mean difference were estimated for the comparison of alogliptin and alogliptin with lansoprazole. A P value of less than 0.05 was accepted as indicating statistical significance (two-sided).

RESULTS

Significant decreases in the HbA1c and FPG levels were obtained in the alogliptin mono-therapy group (n = 26) (7.761 ± 0.6020 to 6.707 ± 0.580%, P < 0.0001 in HbA1c ; 161.8 ± 37.1 to 138.4 ± 42.1 mg/dL, P = 0.0042 in FPG). A significant decrease in HbA1c and a tendency toward a decrease in FPG levels were observed in the combination treatment group (n = 26) (7.819 ± 0.5959 to 6.696 ± 0.6526%, P < 0.0001 in HbA1c ; 164.2 ± 38.6 to 152.7 ± 37.8 mg/dL, P = 0.1414 in FPG). However, there was no significant difference in the change in both HbA1c and FPG levels at the initiation of therapy and at the final visit in the observation-period be-

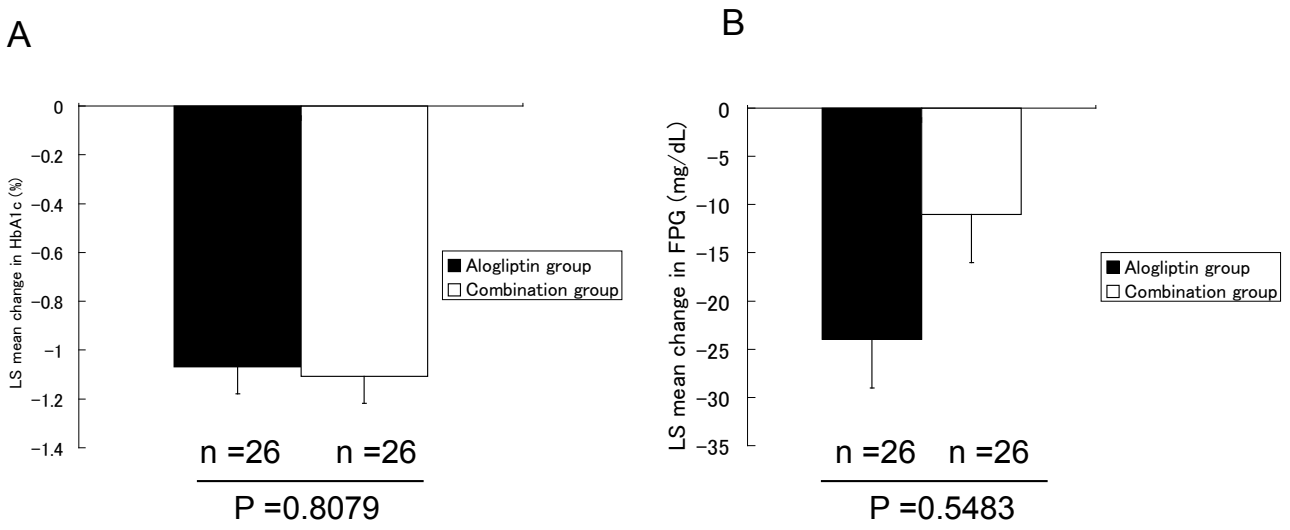

Fig. 1 The effect on HbA1c (**A**) and FPG (**B**) by therapy

In Fig1-5, patients in alogliptin group continued alogliptin-intake during 16 months-observation periods and patients in combination group continued alogliptin-intake during 16 months-observation periods and, as a rule, discontinued lansoprazole-intake 3 months after the initiation of intake of lansoprazole except for 4 patients who continued lansoprazole-intake because of patient's request.

tween the two groups using ANCOVA. The LS mean differences with standard error (SE) of HbA1c at both the initial and final observation points were −1.054±0.548% in the alogliptin mono-therapy group and −1.123±0.723% in the combination group (P=0.8079). Similarly, the LS mean differences with SE of FPG was −23.5±38.0 mg/dL in the alogliptin mono-therapy group and −11.5±38.7 mg/dL in the combination group (P=0.1826) (Figure 1A, B). In a subgroup in which all diabetic drugs were not changed during the observation period (18 patients in the alogliptin mono-therapy group and 17 in the combination group), there was a significant decrease in HbA1c and FPG levels in the alogliptin mono-therapy group (7.666±0.4887 to 6.744±0.5903%, P<0.0001 in HbA1c ; 166.5±36.2 to 147.4±39.4 mg/dL, P=0.0312 in FPG). In the combination group in the subgroup, HbA1c was significantly reduced (7.741±0.4545 to 6.718±0.6921%, P<0.0001), but no change in FPG was found (164.4±40.4 to 155.4±43.8 mg/dL, P=0.3519). There was no significant difference in the change in both HbA1c and FPG levels at initiation of therapy and at the final visit in the observation period between the two groups using ANCOVA. The LS mean differences with SE of HbA1c at both the initial and final observation points were −0.924±0.111% in the alogliptin mono-therapy group and −1.021±0.114% in the combination group (P=0.5483). Similarly, the LS mean differences with SE of FPG were -18.6±8.4 mg/dL in the alogliptin mono-therapy group and -9.5±8.6 mg/dL in the combination group (P=0.4530) (Figure 2A, B).

Furthermore, in the combination group in this subgroup, when the patients were divided into 2 groups in whom lansoprazole was discontinued (n=14), and in whom lansoprazole was continued at the patients' request (n=3), a significant decrease in both HbA1c and FPG levels was obtained in the discontinued group (7.74±0.47 to 6.91±0.88%, P=0.0002 in HbA1c ; 159.1±42.0 to 131.3±26.6 mg/dL, P=0.0067 in FPG). In the continued group in this subgroup, HbA1c was significantly decreased (7.73±0.416 to 6.866±0.321 %, P=0.0270), while no significant decrease in FPG was obtained (189.3±20.6 to 140.0±39.7 mg/dL, P=0.2198). The LS mean differences with SE of HbA1c at the initial and final observation points were −1.100±0.542% in the discontinued group and -0.667±0.603% in the continued group (P=0.2515). Similarly, the LS mean differences with SE of FPG were −3.6±10.4 mg/dL in the discontinued group and −35.1±23.2 mg/dL in the continued group (P=0.2399) (Fig 3A, 3B). The time series effect on HbA1c in the patients who continued to take alogliptin for more than 1

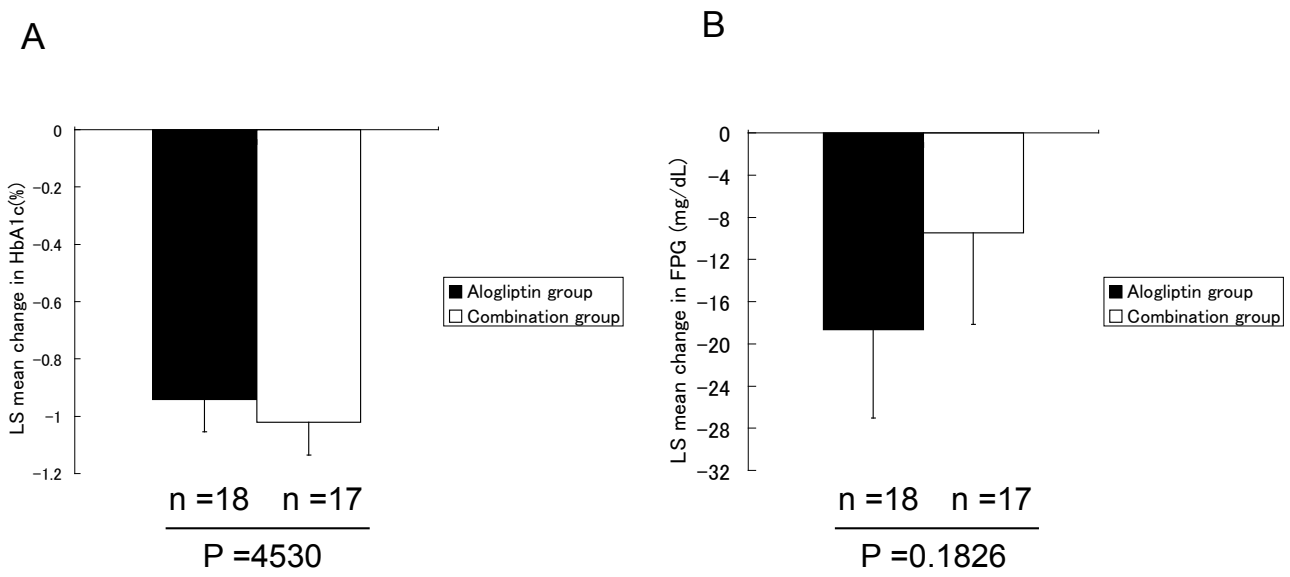

Fig. 2 The effect on HbA1c (**A**) and FPG (**B**) by therapy in a subgroup in which all diabetic drugs were not changed in observation-periods.

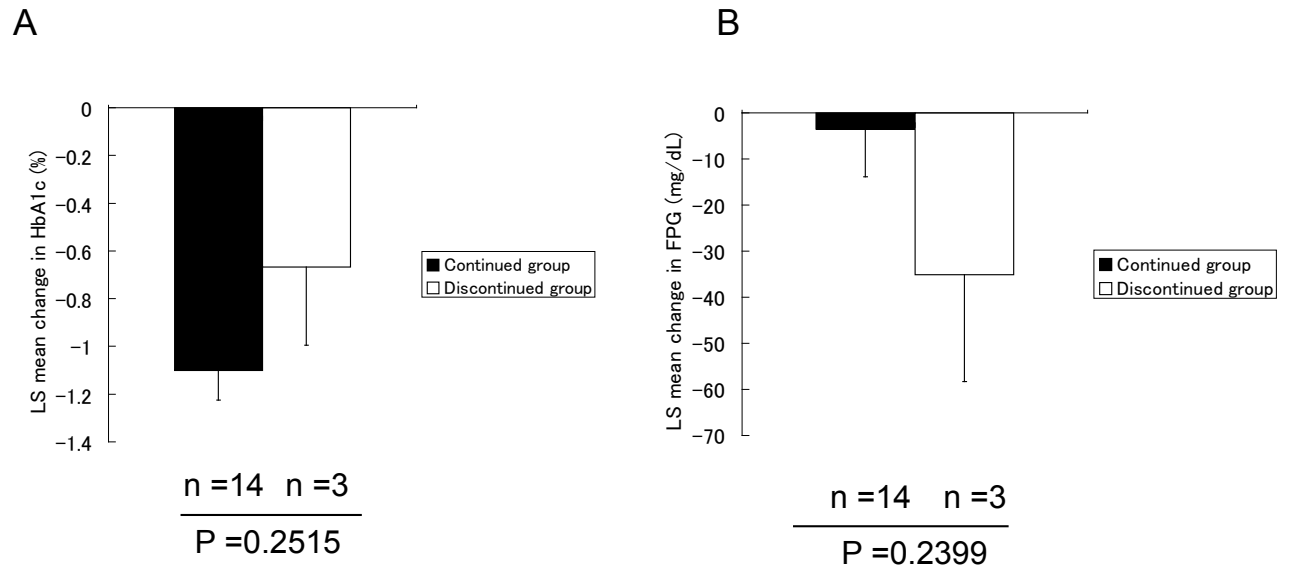

Fig. 3 The effect on HbA1c (**A**) and FPG (**B**) by therapy in combination group in a subgroup in which all diabetic drugs were not changed in observation-periods : Comparison with patients with (n=3) and without (n=14) lansoprazole.

year after enrollment in the APPLE study and in the subgroup patients where all diabetic drugs were not changed during the observation period is shown in Fig. 4A, B, and 5A, B.

DISCUSSION

In the APPLE study, we compared the effect of the combination therapy of alogliptin (a DPP4-I) and lansoprazole (a PPI) with the alogliptin mono-therapy on glycemic control for 3 months in patients with type 2 diabetes[29]. Contrary to our expectation, the effect of the combination therapy on glycemic control was equal to that of the alogliptin mono-therapy. However, because the effect on glycemic control by PPI together with DPP4-I might become apparent only after a relatively long-term use based in part on the expected in-

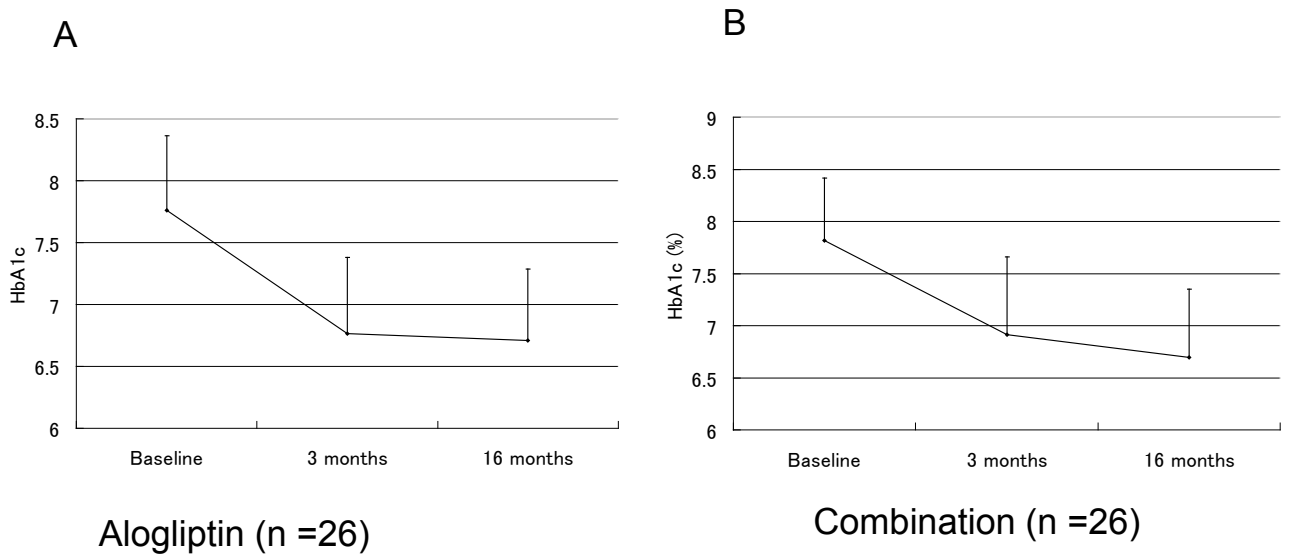

Fig. 4 The time series effect on HbA1c by alogliptin therapy (**A**) and combination therapy (**B**)

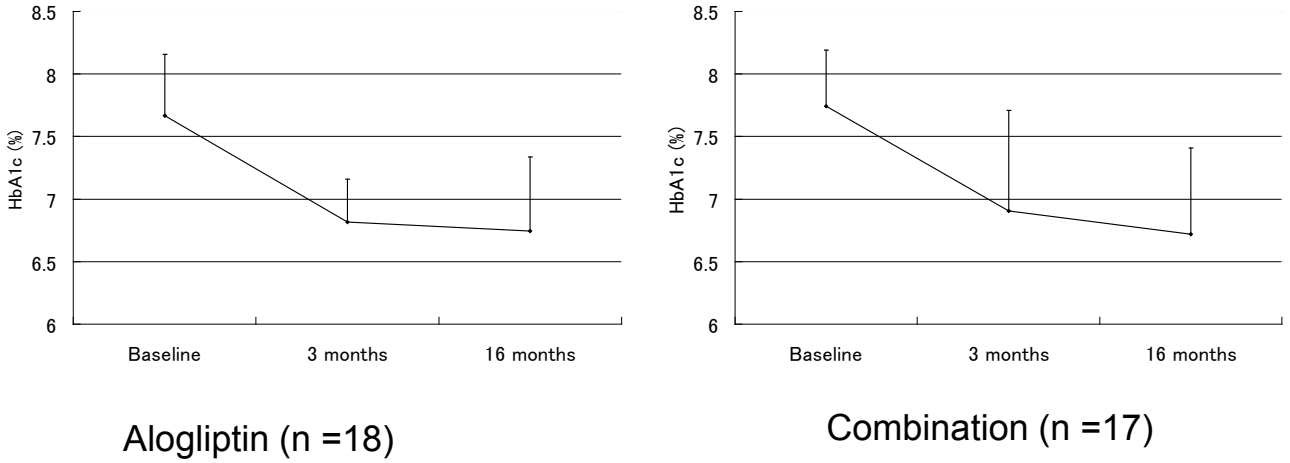

Fig. 5 The time series effect on HbA1c by alogliptin therapy (**A**) and combination therapy (**B**) in a subgroup in which all diabetic drugs were not changed in observation-periods.

creased β cell mass by neogenesis in ductal cells, we performed the current retrospective analysis after the completion of the APPLE study. However, there were no significant differences in either HbA1c or FPG levels between both groups when examined at more than 9 months after the completion of the APPLE study. The dose and type of diabetic drugs were changed in some patients after the completion of the APPLE study, and therefore this may have partially influenced the results. However, even when the patients were limited to a subgroup in which all diabetic drugs were not changed during the observation period, no significant differences in both HbA1c and FPG levels were observed between these groups. Thus, we concluded that the "so called" legacy effect on glycemic control by PPI together with DPP4-I is not apparent at least clinically in patients with type 2 diabetes. It is difficult to explain exactly the reason for the negative results of this APPLE study and the additional retrospective analysis, because in animal models the synergic effect of the combination of PPI and DPP4-I (or a GLP-1 receptor agonist) on glycemic control and on an increase of β cell mass is clearly shown[17,18,30]. One possible reason may be that the elevation of serum gastrin levels by PPI therapy was insufficient to provide a clinically observable glucose-lowering effect. In the APPLE study, the elevation of serum gastrin levels was approximately two-fold in the combination therapy group

compared with that in the alogliptin mono-therapy group[29]. This seems to be large as the elevation of gastrin by PPI since, in the study by Singh et al., in which positive results were obtained, the increase of gastrin by PPI (pantoprazole) was only approximate 1.5-fold [24], which was accompanied with an increase of insulin. However, in *Psammomys obesus*, a model of type 2 diabetes, PPI therapy improved glycemic control accompanied by an increase in plasma insulin and in β cell mass only when PPI was used at a very high dose (lansoprazole 10-15 mg/kg) and gastrin was elevated nine-fold[31]. In that study, PPI was used as a mono-therapy, and the combination therapy with DPP4-I was not tested. Therefore, although the conditions differ from that in our study, we speculate that the degree of the elevation of gastrin induced by PPI is dose-dependent and is important to obtain the full glucose-lowering effect. Because it is reported that vonoprazan (a new generation PPI : potassium-competitive acid blocker) is more effective for inhibition of gastric acid and elevates serum gastrin to higher levels (approximately six- to seven-fold with 10-40 mg of vonoprazan) compared with that of the existing PPI[32], it would be interesting to investigate in the future whether this agent would be more effective on glycemic control. Another possible reason for our results may be attributed to the selection of DPP4-I (but not a GLP-1 receptor agonist) used in combination with PPI. It is reported that combination therapy with a PPI and a DPP4-I more effectively improved hyperglycemia than mono-therapy by each treatment separately in NOD mice[17]. However, because in general the elevation of GLP-1 by the administration of DPP4-I is lower than that by a GLP-1 receptor agonist, logically the use of a GLP-receptor agonist in combination therapy appears to be more suitable. There were no clinical studies with the combination therapy of a PPI and a GLP-1 receptor agonist in patients with type 2 diabetes as well as type 1 diabetes until now. This therapy appears to be attractive, and future studies are warranted to confirm the effect of this combination therapy.

In this study, we also found that, in a subgroup in which all diabetic drugs were not changed during the observation period, there was no significant difference in the change of HbA1c and FPG levels between patients who continued to take lansoprazole and those who discontinued it after completion of the 3 month APPLE study. Although the number of patients who continued to take lansoprazole (n = 3) was very small, this finding also suggests that the add-on effect of a PPI to DPP4-I is not apparent at least clinically in patients with type 2 diabetes. However it should be noted that these 3 patients had had epi-gastric symptoms before enrollment in the APPLE study, and that the symptoms improved after administration of PPI. This may bias the findings because it is possible the treatment increased the appetite of these patients, and therefore influenced glycemic control.

In the current study, we also noted that the improvement in HbA1c by alogliptin is maintained relatively long-term (approximately 16 months). This result appears to support the results of a recently published study, in which the improvement on glycemic control by alogliptin lasted long-term (2 years)[33].

In the current study because of the retrospective observational analysis, we could not evaluate serum gastrin levels, which are important to discuss the possible legacy effect of PPI together with DPP4-I on glycemic control. This is one of the limitations in this study.

In conclusion, based on the results in the APPLE study and in the retrospective observation in the current study, we conclude that the add-on effect of a PPI for DPP4-I on glycemic control in patients with type 2 diabetes is not apparent clinically. A combination therapy using a new generation PPI, such as vonoprazan and a GLP-1 receptor agonist, in patients with type 2 diabetes might be more effective on glycemic control, and future studies are warranted to determine the effect of this combination therapy.

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