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Changes in medication adherence and unused drugs after switching from daily dipeptidyl peptidase-4 inhibitors to once-weekly trelagliptin in patients with type 2 diabetes

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ABSTRACT

Aims: The changes in patients' satisfaction with the treatment, medication adherence and unused drugs before and after switching from daily DPP-4 inhibitors to once-weekly trelagliptin administration were prospectively investigated in patients with type 2 diabetes.
Methods: After excluding 46 patients who declined to switch from daily DPP-4 inhibitors, 79 subjects were included in the present study. The clinical parameters and results of questionnaire surveys regarding satisfaction with treatment as well as impressions of the amount of medicine/number of doses, medication adherence, and unused drug were examined at the baseline and 3 months after switching from daily DPP-4 inhibitors to trelagliptin in 75 patients with type 2 diabetes.
Results: Although the value of HbA1c did not change (7.0% ± 0.5% to 7.0% ± 0.6%), the scores representing satisfaction with the treatment (25.2 ± 6.4 to 26.4 ± 6.0), impression of the amount of medicine (−0.3 ± 1.0 to 0.3 ± 1.0) and number of doses (0.3 ± 1.0 to 0.8 ± 0.6), and medication adherence (0.8 ± 0.4 to 0.9 ± 0.3) as assessed by the questionnaire surveys were significantly improved after switching from DPP-4 inhibitors. The self-reported amount of unused drugs was significantly reduced after switching.
Conclusions: Switching from daily DPP-4 inhibitors to once-weekly trelagliptin improved the satisfaction with the treatment, impression of the prescribed medicine and medication adherence in the type 2 diabetic patients who expresses a desire to reduce their prescription medicines. In such patients, improvements in the glycemic control and long-term prognosis might be expected through the reduction of unused drugs.

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1. Introduction

Medication adherence is important in drug therapy for lifestyle-related diseases. However, non-adherence to the medication, resulting in unused drugs, is occasionally found in the treatment of type 2 diabetes [1–3]. We previously reported that unused drugs were prone to occur when the patients with type 2 diabetes felt that the number of drugs they had been prescribed was too many [4]. Furthermore, medication adherence is independently influenced by patient age, sex, education level, and income [4,5]. Non-adherence to medication is closely related to a deterioration in glycemic control [6,7] and an increase in mortality among patients with diabetes [8].

Sitagliptin, the first dipeptidyl peptidase-4 (DPP-4) inhibitor, was released in 2009, and seven daily-administration DPP-4 inhibitors are currently available in Japan [9]. The prescription rate of DPP-4 inhibitors ranges from 60% to 70% in the clinical setting [9,10] because of the lack of associated weight gain, safety in cases with renal insufficiency [11], and low frequency of severe hypoglycemia caused by antidiabetics, such as sulfonylureas and insulin preparations [12]. This trend in the prescription rate of antidiabetic agents is different from that in the Western countries [13,14] and considered to be unique to Japan. The first once-weekly DPP-4 inhibitor, trelagliptin, has been available in Japan since 2015. Trelagliptin reportedly showed similar efficacy and safety to once-daily alogliptin in Japanese patients with type 2 diabetes in the phase 3 trials [15,16]. Furthermore, there were no significant differences in the incidence of adverse events between Japanese patients with type 2 diabetes who received add-on therapy of once-weekly trelagliptin to insulin monotherapy and those who received placebo as add-on therapy to insulin for a 12-week double-blind phase 4 trial [17]. The blood glucose level was not markedly changed at 12 weeks after switching from once-daily sitagliptin therapy to once-weekly trelagliptin [18].

It was reported that postmenopausal women prescribed a once-weekly regimen of bisphosphonates for the treatment of osteoporosis had significantly greater rates of compliance than those prescribed a daily regimen [19]. Similarly, once-weekly glucose-lowering medication is received positively by patients with type 2 diabetes administered oral antidiabetic drugs [20]. Therefore, switching from daily DPP-4 inhibitors to once-weekly trelagliptin may improve the glycemic control in real practice through better medication adherence than was observed in the phase 3 trial [18].

For this reason, we investigated the changes in the glycemic control, medication adherence, patients' satisfaction with the treatment, and unused drugs before and after switching from daily DPP-4 inhibitors to once-weekly trelagliptin administration.

2. Methods

2.1. Patients

The current prospective study was performed between January 2017 and March 2018 at the Department of Diabetes, Metabolism and Kidney Disease, Edogawa Hospital (Tokyo, Japan). It was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committees of Edogawa Hospital (approved number: 2016–56, date: September 3, 2016). Written informed consent was obtained from every participant.

The flowchart of patients' selection is shown in Fig. 1. Initially, 478 type 2 diabetic patients under the administration of daily DPP-4 inhibitors for more than 3 months between January and December 2017 were extracted as candidates for this study. After excluding the subjects with renal impairment (males with serum creatinine levels >1.4 mg/dL or females with serum creatinine levels >1.2 mg/dL), whose HbA1c level >9.0% or <6.0%, cognitive dysfunction, and/or obvious non-adherence to the medication based on the physician's judgment, 125 patients were considered eligible for the study and received information on switching from daily DPP-4 inhibitors to once-weekly trelagliptin. Forty-six patients declined to participate, and 79 patients (63%) expressed a desire to switch. The reluctance of 46 patients to switch from DPP-4 inhibitors was due to concerns about forgetting to take trelagliptin, or about taking trelagliptin daily like other prescribed medicines. Because the physicians explained about the safety of trelagliptin compared with other DPP-4 inhibitors, no subjects were concerned about drug related adverse events. Finally, 75 patients who were able to respond to questionnaire surveys at the prescription date of trelagliptin (baseline) and three months after switching were investigated in the present study.

The subjects were administered trelagliptin (Zafatek® tablets; Takeda Pharmaceutical Company Ltd., 100 mg once a week) instead of the previously prescribed daily DPP-4 inhibitors without changing any other drugs at the start of the study. The clinical parameters and laboratory data were evaluated at the prescription date of trelagliptin and three months after switching in each subject.

2.2. Questionnaire surveys

At baseline and three months after the initiation of trelagliptin, the Diabetes Treatment Satisfaction Questionnaire (DTSQ) was administered in order to assess the influence of treatment on the patients' quality of life [21,22]. The DTSQ scores were analyzed separately for treatment satisfaction and perceived hyperglycemia/hypoglycemia. Treatment satisfaction was estimated by scoring questions 1, 4, 5, 6, 7 and 8 of the DTSQ. Perceived hyperglycemia and hypoglycemia were expressed as the scores of questions 2 and 3, respectively. Other questionnaire surveys to evaluate the impression of the amount of medicine (Q1) and number of doses (Q2), medication adherence (Q3), and unused drugs (Q4) were scored as described below.

Q1. How do you feel about the amount of medicine you are prescribed?
1. Just right or not too much = +1 point
2. Too much = −1 point

Q2. How do you feel about the number of doses you must take?
1. Just right or not too many = +1 point
2. Too many = −1 point

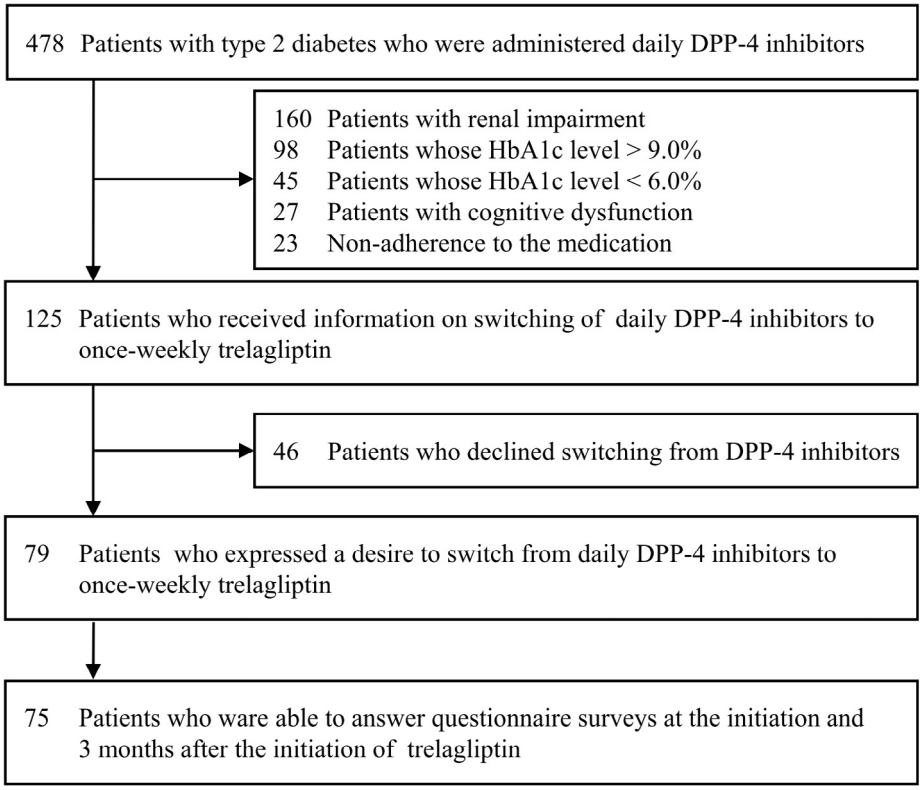

Fig. 1 – Flowchart of patients' selection.

Q3. Are you taking medicines in accordance with your doctor's instructions?

1. Yes, I precisely take my medication = +1 point
2. Usually, but sometimes I forget to take my medicine = 0 point
3. No, I have not taken much or hardly taken my medicine = −1 point

Q4. Do you have any unused drugs despite receiving a prescription?

1. No, I have no or almost no unused drugs = +1 point
2. Yes, I have some unused drugs = 0 point
3. Yes, I have quite a few unused drugs = −1 point

The number of prescribed drugs included medicine from all departments of our hospital. The drugs prescribed by other hospitals were excluded from the present study because they may not have been accurately determined. Medicines for use as needed and for external use were also excluded. Regarding the number of doses, dosing before meals, after meals, between meals and before bedtime were calculated as one dose each.

2.3. *Statistical analysis*

All of the data are presented as the mean ± standard deviations. Wilcoxon's signed rank test was used to determine the presence of differences in the clinical characteristics and the scores obtained from the questionnaire surveys compared with the baseline values. A least squares model was used to evaluate the associations between the changes in the scores for unused drugs and the clinical background factors of the patients. Differences with a P value of <0.05 (two-tailed) were considered to be statistically significant. The statistical software package JMP version 8.0.1 (SAS Institute, Cary, NC, USA) was used to perform all analyses.

3. Results

3.1. *Clinical and laboratory characteristics before and after switching from DPP-4 inhibitors*

Men accounted for 49% of study subjects. The mean patient age and duration of diabetes was 69 ± 9 years and 14 ± 10 years, respectively. The mean number of oral drugs and doses was 5.4 ± 2.6 and 2.3 ± 1.3, respectively. Injection preparations (insulin or glucagon-like peptide-1 receptor agonists) were prescribed in 10 patients. Sitagliptin, vildagliptin, alogliptin, linagliptin, and teneligliptin were administered in 28, 8, 8, 19 and 12 patients, respectively, before switching from DPP-4 inhibitors.

The changes in the clinical and laboratory characteristics are shown in Table 1. No parameters, including the HbA1c value, changed significantly after switching from daily DPP-4 inhibitors. Severe hypoglycemia requiring the assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions was not observed during the study period.

Table 1 – The changes in clinical parameters of the patients.

	Before	After	P
Body weight (kg)	64.6 ± 14.0	64.8 ± 13.9	0.40
Body mass index (kg/m^2)	24.8 ± 3.9	24.9 ± 3.8	0.42
Systolic blood pressure (mmHg)	129 ± 10	131 ± 11	0.13
Diastolic blood pressure (mmHg)	74 ± 9	75 ± 10	0.47
HbA1c (%)	7.0 ± 0.5	7.0 ± 0.6	0.22
HbA1c (mmol/mol)	53 ± 6	53 ± 7	0.22
LDL-cholesterol (mg/dL)	94 ± 24	93 ± 23	0.94
HDL-cholesterol (mg/dL)	55 ± 16	56 ± 17	0.23
Non HDL-cholesterol (mg/dL)	120 ± 27	119 ± 26	0.93
Serum creatinine (mg/dL)	0.77 ± 0.19	0.75 ± 0.18	0.51
Serum uric acid (mg/dL)	5.0 ± 1.1	4.9 ± 1.0	0.18

LDL, low-density lipoprotein; HDL, high-density lipoprotein.

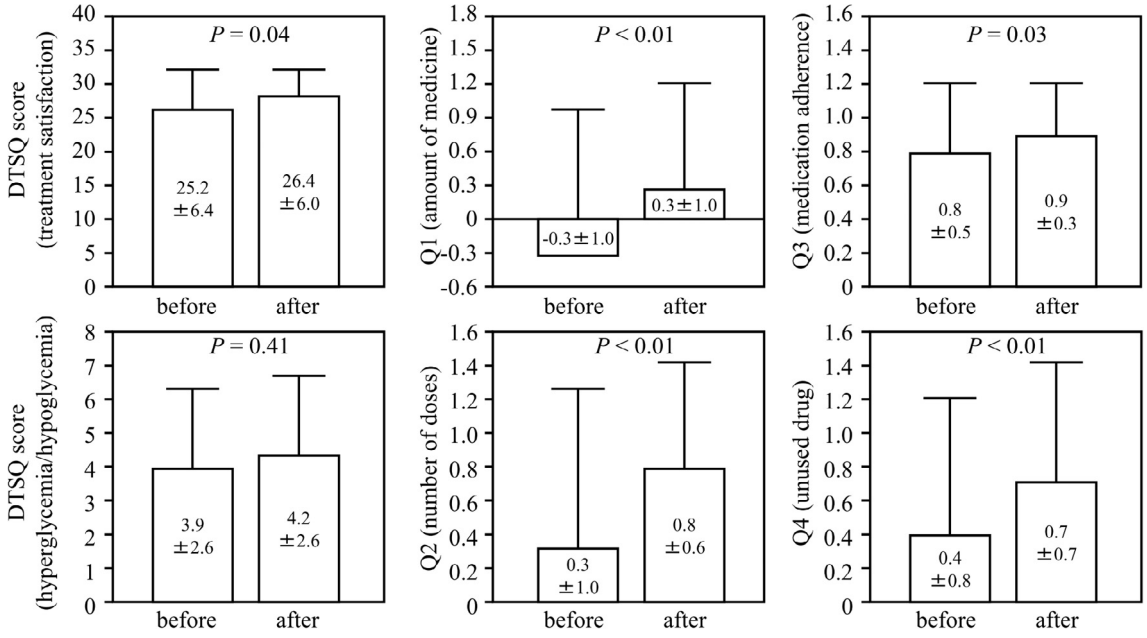

Fig. 2 – Scores obtained from the questionnaire surveys, including the DTSQ, before and after switching from daily DPP-4 inhibitors to once-weekly trelagliptin.

3.2. *Scores of questionnaire surveys before and after switching from daily DPP-4 inhibitors*

Fig. 2 shows the scores obtained from the questionnaire surveys, including the DTSQ, before and after switching from daily DPP-4 inhibitors. Although perceived hyperglycemia or hypoglycemia of the DTSQ did not significantly differ after switching, the score representing treatment satisfaction significantly increased. The scores representing the impression of the amount of medicine and number of doses, medication adherence, and unused drugs also improved significantly after switching.

3.3. *Association of the changes in unused drug and clinical background factors*

Table 2 shows the association of the changes (the value at three months after switching minus the value at baseline) in the score representing unused drugs and clinical background factors at the baseline. Although this change was not significantly associated with any clinical background factors of the patients, it showed a significantly negative correlation with the scores representing medication adherence and unused drugs obtained from the questionnaire surveys. Furthermore, this change was significantly associated with only the score representing unused drugs (regression coefficient = −0.707, $P < 0.01$) after a multivariate analysis using the scores representing medication adherence and unused drugs as independent variables.

3.4. *Relationships between the change in the HbA1c values and the scores representing medication adherence and unused drug*

The change in the HbA1c value showed a significantly negative correlation with the change in the score representing unused drugs (Fig. 3).

Table 2 – The association of the changes in the scores for unused drugs and clinical parameters at the baseline.

	Regression coefficient	P
Male sex	0.084	0.66
Age (years)	0.004	0.73
Duration of diabetes (years)	0.009	0.36
Number of oral drugs	−0.004	0.92
Number of doses	−0.011	0.88
Body weight (kg)	0.000	0.95
Body mass index (kg/m^2)	−0.002	0.92
Systolic blood pressure (mmHg)	0.009	0.32
Diastolic blood pressure (mmHg)	0.008	0.45
HbA1c (%)	0.264	0.16
HbA1c (mmol/mol)	0.024	0.16
LDL-cholesterol (mg/dL)	0.000	0.93
HDL-cholesterol (mg/dL)	0.001	0.87
Non HDL-cholesterol (mg/dL)	0.001	0.81
Serum creatinine (mg/dL)	−0.442	0.39
Serum uric acid (mg/dL)	0.052	0.54
DTSQ (treatment satisfaction)	0.024	0.15
DTSQ (hyperglycemia/hypoglycemia)	0.030	0.47
Q1 (amount of medicine)	0.021	0.64
Q2 (number of doses)	0.011	0.91
Q3 (medication adherence)	−0.561	<0.01
Q4 (unused drugs)	−0.708	<0.01

LDL, low-density lipoprotein; HDL, high-density lipoprotein.

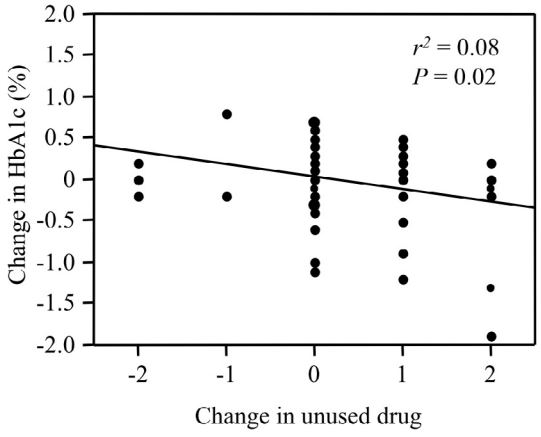

Fig. 3 – Relationships between the changes in the HbA1c values and the score representing unused drugs obtained from the questionnaire survey.

4. Discussion

Although the values of HbA1c, body weight, and serum lipid concentrations did not change markedly, the scores representing treatment satisfaction and medication adherence significantly improved after switching from daily DPP-4 inhibitors to once-weekly trelagliptin in the present study. Because the current study was conducted for a short period, the metabolic factors described above were considered to be similar before and after switching. However, the long-term glycemic control and patients' prognosis might be improved if the reduction in unused drugs observed in the current study continues for a long time.

Many patients with type 2 diabetes express a desire to reduce the number of drugs they are prescribed in real practice [19,23]. Although the dosing pattern of only a single drug was reduced from daily to weekly in the present study, this change significantly improved patients' impressions of the amount of medicine and number of doses. Negative impressions by patients concerning prescriptions are closely related to non-adherence to diabetes treatment [4,24,25]. Because DPP-4 inhibitors show a better glucose-lowering efficacy in Asians than in other ethnic groups [26], the prescription rate of DPP-4 inhibitors has been high in the Japanese clinical setting [9,10]. Improved adherence to prescribed therapies, including DPP-4 inhibitors, might contribute to a better prognosis of Japanese patients with type 2 diabetes through the reduction of unused drugs. The drug price of a trelagliptin 100 mg tablet is 995 yen in Japan. There is not much difference in the daily cost when daily DPP-4 inhibitors are used. However, benefits in terms of medical expenses can be expected in addition to improvement of the long-term prognosis in patients with type 2 diabetes if unused drugs are reduced by switching from daily DPP-4 inhibitors to the once-weekly trelagliptin. It was previously reported that antidiabetic therapy using fixed-dose combination products improved treatment satisfaction [27] and medication adherence [28,29] in patients with type 2 diabetes. Switching from daily DPP-4 inhibitors to once-weekly trelagliptin is considered to cause a similar change in the impression of prescribed drugs.

However, there is concern that switching from daily DPP-4 inhibitors to once-weekly trelagliptin may conversely complicate the dosing regimen. Most patients are prescribed multiple drugs [30] because diabetic patients frequently have co-morbidities, such as hypertension, dyslipidemia, and obesity [31]. Because these patients take other medicines besides trelagliptin daily, they might forget to take trelagliptin at all, or instead take trelagliptin daily like other medicines. To

avoid such medication errors, we excluded subjects with cognitive dysfunction and non-adherence at the selection of the study subjects. Furthermore, we explained to candidate participants that such confusion might occur after switching from DPP-4 inhibitors to once-weekly trelagliptin. The patients who declined to switch from daily DPP-4 inhibitors before enrolling in the current study (46/125 = 37%) were considered to be the group concerned about the above-mentioned errors. Switching of DPP-4 inhibitors to once-weekly trelagliptin might not be the best method for all diabetic patients who are prescribed DPP-4 inhibitors. This approach should therefore be positioned as a treatment option tailored to the patients who wish to reduce the number of medicines they are prescribed.

Patients in whom switching from daily DPP-4 inhibitors to once-weekly trelagliptin is most appropriate seem to be limited, as many patients were initially excluded from the present study. Our department covers nephrology, and the frequency of renal impairment is higher in the patients we manage than in other medical institutions for the treatment of diabetes [32–35]. Therefore, approximately one-third of the candidates were excluded due to renal impairment in the current study. More subjects are likely to be eligible to switch from daily to weekly DPP-4 inhibitors in a real-world clinical setting.

Several limitations associated with this study warrant mention. First, this study was conducted in a relatively small number of patients for a short duration. Long-term observation is necessary because whether or not the improved adherence observed in the present study could be maintained for a long time was unclear. Second, the number of unused drugs was based solely on the self-report of the patients in this study. We cannot deny the possibility that subjects gave convenient answers to the questionnaire surveys after switching because they knew the purpose of the present study. It should be also noted that the actual decrease in unused drugs was not examined directly. Third, the patients judged to have obvious non-adherence to the medications were excluded from the present study, although such subjects were relatively rare. Because switching from daily DPP-4 inhibitors to once-weekly trelagliptin may be a potential strategy for improving medication adherence especially in such patients, another investigation in subjects with non-adherence to the medication should be conducted.

5. Conclusion

Switching from daily DPP-4 inhibitors to once-weekly trelagliptin improved the satisfaction with the treatment, medication adherence, and impression of the prescribed medicines among type 2 diabetic patients who expressed a desire to reduce their prescription medicines. In such patients, improvements in the glycemic control and long-term prognosis might be expected through the reduction of unused drugs.

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Declaration of Competing Interest

Hiroyuki Ito has received lecture fees from Takeda Pharmaceutical Company Ltd., Sanofi KK, Eli Lilly Japan KK, Novo Nordisk Pharma Ltd., MSD KK, Novartis Pharma KK, Astellas Pharma, Daiichi Sankyo Company, Boehringer Ingelheim, Terumo Corporation, Mochida Pharmaceuticals, Teijin Pharma, Kissei Pharmaceuticals, Kowa Pharmaceuticals, Mitsubishi Tanabe Pharma Corporation, Sanwa Kagaku Kenkyusho, Dainippon Sumitomo Pharma, AstraZeneca KK, Kyowa Hakko Kirin, Shionogi and Co, Taisho Toyama Pharmaceutical Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Bayer Yakuhin, Ltd., and Santen Pharmaceutical Co., Ltd., and has received consulting fee from Becton, Dickinson and Company. Shigenori Ando has received lecture fees from Takeda Pharmaceutical Company Ltd. Suzuko Matsumoto has received lecture fees from Novo Nordisk Pharma Ltd., Astellas Pharma, and AstraZeneca KK. Shinya Nishio has received lecture fees from Sanofi KK, Taisho Toyama Pharmaceutical Co., Ltd., Kyowa Hakko Kirin, Bayer Yakuhin, Ltd., and Mitsubishi Tanabe Pharma Corporation. Shinichi Antoku has received lecture fees from Kyowa Hakko Kirin, Sanofi KK, Kyowa Hakko Kirin, Taisho Toyama Pharmaceutical Co., Ltd., Daiichi Sankyo Company, and Otsuka Pharmaceutical Co., Ltd. Emiko Tsugami, Rie Araki, Eiji Kusano, Kosuke Uemura, Tomoko Yamasaki, Toshiko Mori, and Michiko Togane have no conflict of interest.

Author contributions

HI contributed to conception, design, analysis, interpretation, writing first draft, editing, and final approval. SA contributed to reviewing drafts, editing, and final approval. ET, RA, EK, SM, KU, SN, SA, TY, TM and MT contributed to data collection and final approval.

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