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STUDY PROTOCOL

Study Protocol for the Initial Choice of DPP-4 Inhibitor in Japanese Patients with Type 2 diabetes Mellitus: Effect of Linagliptin on QOL (INTEL-QOL) Trial

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ABSTRACT

Introduction: Consideration of treatment-related quality of life (QOL) is important in diabetes management. However, no studies have compared the influence of dipeptidyl peptidase-4 inhibitors versus metformin on treatment-related QOL when used as first-line therapy in patients with type 2 diabetes mellitus.

Methods: This study is a prospective, randomized, open-label, multicenter, parallel-group, comparative study. Between June 2016 and December 2017, 44 participants who failed to achieve glycemic control despite diet and exercise therapy were recruited at 14 clinics and randomly allocated to linagliptin or metformin therapy. Treatment-related QOL was assessed with the Oral Hypoglycemic Agent Questionnaire, version 2 (OHA-Q ver. 2) and the self-administered Diabetes Therapy-Related QOL (DTR-QOL) questionnaire. The primary study outcome is the difference in total OHA-Q ver. 2 score between the two treatment groups at the end of the study. The secondary outcomes include differences in the scores for each OHA-Q ver. 2 subscale between the two treatment groups at the end of the study, change in total DTR-QOL score and for each domain from baseline to the end of treatment, changes in glycemic control, and adverse events.

Planned outcome: The present study is designed to assess the effects of linagliptin on the treatment-related QOL. Results will be available in the near future. Study findings are expected to provide useful information on how to maintain or improve QOL in patients with type 2 diabetes mellitus treated with insulin.

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INTRODUCTION

One of the main objectives of diabetes management is to maintain quality of life (QOL) by preventing development or progression of complications [1]. In patients with type 2 diabetes mellitus (T2DM), advanced age, poor glycemic control, previous hypoglycemic episodes, and complex therapies are associated with lower QOL [2–5]. On the other hand, intensive frequency of follow-up was associated with improvements of QOL [6]. Given that decreased treatment-related QOL is associated with reduced patient motivation and adherence to treatment in patients with T2DM [7], consideration of treatment-related QOL is important when choosing oral anti-hypoglycemic agents (OHAs).

Treatment guidelines by the American Diabetes Association and European Association for the Study of Diabetes recommend metformin as first-line therapy when lifestyle modification alone fails to achieve or maintain optimal glycemic goals [8]. Metformin reduces blood glucose levels by improving insulin sensitivity, mainly in the liver. Metformin has an established evidence base showing that it is efficacious in lowering blood glucose levels without increasing the risk of hypoglycemia, with weight neutrality or loss. In addition, metformin is generally safe, well tolerated, and inexpensive [9]. Metformin might also reduce the incidence of cardiovascular events and improve survival [10]. However, a recent meta-analysis demonstrated that adherence to metformin was worse than for other OHAs such as sulfonylureas and thiazolidinediones [11]. In this regard, the most common adverse effects of metformin are gastrointestinal effects, such as nausea, vomiting, and diarrhea [12]. These symptoms might reduce patient adherence to metformin treatment. In addition, given that a sustained release preparation of metformin is not available in all countries, the need to take metformin more than twice daily may negatively affect patient adherence to therapy. These characteristics of metformin might reduce treatment-related QOL.

Conversely, the Japan Diabetes Society treatment guidelines recommend choosing suitable therapies in line with the dominant pathophysiological condition of each patient, such as insufficient insulin secretion or insulin resistance [13], because T2DM in East Asians is more strongly associated with beta cell dysfunction than insulin resistance and adiposity [14]. In this context, various types of OHAs, including metformin and dipeptidyl peptidase (DPP)-4 inhibitors, are chosen as first-line therapy in Japan [15].

DPP-4 inhibitors such as linagliptin enhance glucose-dependent insulin secretion from pancreatic beta cells via inhibiting the degradation of active incretins by DPP-4. In general, DPP-4 inhibitors are safe and well tolerated and do not cause weight gain [16]. Sitagliptin was shown to improve QOL in a single arm-study [17]. Owing to these characteristics, DPP-4 inhibitors are now the most frequently prescribed first-line agents for T2DM in Japan [18].

In this study, to investigate how these treatment regimens affect QOL of patients with T2DM, we evaluated the effect of linagliptin versus metformin on treatment-related QOL using the Oral Hypoglycemic Agent Questionnaire, version 2 (OHA-Q ver. 2) and the self-administered Diabetes Therapy-Related QOL (DTR-QOL) questionnaire [19]. Although these questionnaires are newly developed, they are valid [19, 20].

MATERIALS AND METHODS

Study Design

The Initial choice of DPP-4 inhibitor in Japanese T2DM patients: Effect of Linagliptin on QOL (INTEL-QOL) study is a prospective, randomized, open-label, multicenter, parallel-group, comparative trial. This study is planned solely to evaluate the QOL. This study has been registered on the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR), a non-profit organization in Japan

that meets the requirements of the International Committee of Medical Journal Editors (ICMJE) (UMIN000022953).

Study Population

Japanese patients with T2DM who regularly attended the outpatient diabetes clinics of 14 institutions (Chimori Clinic, Ikeda Clinic, Yamamoto Clinic, Japanese Red Cross Medical Center, Juntendo Tokyo Koto Geriatric Medical Center (Department of Medicine, Diabetology and Endocrinology), Juntendo University Graduate School of Medicine (Department of Metabolism and Endocrinology), Juntendo University Shizuoka Hospital (Department of Diabetes, Endocrinology, and Metabolism), Sawaki Internal Medicine and Diabetes Clinic, Shimizu Clinic, Tanaka Clinic, Menju Clinic, Misaki Naika Clinic, Musashino Family Clinic, and Yasuda Clinic) in Japan were asked to participate in this study. The inclusion criteria are as follows: (1) T2DM not at target blood glucose control as specified in the Treatment Guide for Diabetes by the Japan Diabetes Society [13] despite the introduction of diet and/or exercise therapy; (2) patients who are considered to newly initiate OHAs in addition to dietary and/or exercise therapy; (3) age $\geq$ 20 years and $<$ 75 years, regardless of gender; and (4) written informed consent for study participation. The following exclusion criteria are used: (1) type 1 or secondary diabetes; (2) acute diabetic complications within the past 6 months; (3) congestive heart failure or myocardial infarction requiring pharmacotherapy; (4) unstable angina pectoris or coronary bypass surgery within the past 6 months; (5) chronic cirrhosis or chronic active hepatitis; (6) artificial dialysis or moderate renal dysfunction; (7) aspartate aminotransferase or alanine aminotransferase levels more than three times higher than the upper limit of the normal range; (8) direct bilirubin more than three times higher than the upper limit of the normal range, clinically abnormal thyroid-stimulating hormone level, or fasting triglyceride levels $>$ 7.9 mmol/L; (9) treatment with any type of antidiabetic drug; (10) dementia, possible dementia, or mental disorder; (11) insufficient judgment ability or illiteracy; (12) requiring consent for study participation from a legal representative; (13) pregnancy, lactation, possibly pregnancy, or planning to become pregnant during the study period; (14) history of hypersensitivity to investigational drugs; (15) present or past history of a malignant tumor, unless there was no current medical therapy, no recurrence to date, and no risk of recurrence during this study; and (16) judged as ineligible by the clinical investigators.

The subjects were screened consecutively. Patients that met the above eligibility criteria were asked to participate in the present study. All patients who agreed to participate were enrolled in the study. The protocol has been approved by the institutional review board of each participating institution in compliance with the Declaration of Helsinki and current legal regulations in Japan. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the 1964 Declaration of Helsinki, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

Randomization and Study Intervention

Patients were registered at the INTEL-QOL trial's administration office via the internet. Once enrolled, patients were randomly assigned to either the linagliptin group or the metformin group. Randomization was performed using a dynamic allocation method based on age ($<$ 65 or $\geq$ 65 years) and gender (male or female).

Patients in the linagliptin group were started on linagliptin 5 mg once daily. Patients in the metformin group were started on metformin 500 mg twice daily. The dose of metformin was increased to a maximum dose of 2250 mg once daily when HbA1c was $\geq$ 7.0% [13]. The addition of OHAs other than the study drugs and insulin is not permitted in both groups during the study.

Study Variables and Schedule

The study variables and schedule are shown in Table 1 and Fig. 1. The study period consists of 24 weeks after registration (registration period, June 2016 to December 2017; full study duration, June 2016 to September 2018). All randomized participants will be followed until the end of the scheduled study, regardless of adherence to or discontinuation of the study medication for any reason. Clinical outcome, adherence, and adverse events will be ascertained. Clinical and biochemical data are collected at baseline and 24 weeks after randomization. Blood samples are obtained after overnight fasting at baseline and 24 weeks after randomization. Urinary albumin excretion is measured by latex agglutination assay using a spot urine sample at baseline and 24 weeks after randomization. In addition, participants were asked to record usage of their study drug on a medication record during the study period.

STUDY OUTCOMES

The primary study outcome is the difference in the total OHA-Q ver. 2 score between the two treatment groups at the end of the study. The secondary outcomes are (1) the difference in score for each OHA-Q ver. 2 subscale between the two treatment groups at the end of the study; (2) change in total DTR-QOL score and score for each DTR-QOL domain from baseline to 24 weeks; (3) change in HbA1c from baseline to 24 weeks; (4) differences in the proportion of patients who achieved HbA1c $< 6.0\%$ or $< 7.0\%$ at the end of the study or whose HbA1c levels improved by more than 0.5% from baseline to 24 weeks; (5) change in fasting glucose levels from baseline to 24 weeks; (6) differences in the proportion of patients who achieved HbA1c $<$ 7.0% and had an improved total DTR-QOL score at the end of the study; (7) differences in the prevalence of hypoglycemic events; (8) differences in the proportion of gastrointestinal symptoms such as nausea, vomiting, and

Table 1 Variables and data collection schedule

	Registration	Treatment period		
		Baseline	Baseline to week 24	Week 24
Patient characteristics	○			
Body weight		○		○
Blood pressure		○		○
Blood chemistry[a]		○		○
Urinary albumin excretion		○		○
Oral Hypoglycemic Agent Questionnaire, version 2				○
Diabetes Therapy-Related Quality of Life questionnaire		○		○
Hypoglycemic events		○	○	○
Gastrointestinal events		○	○	○
Other adverse events		○	○	○
Adherence		○	○	○

[a] Includes aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase, total bilirubin, blood urea nitrogen, creatinine, estimated glomerular filtration rate, uric acid, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, fasting plasma glucose, fasting inulin, HbA1c, amylase, and thyroid-stimulating hormone

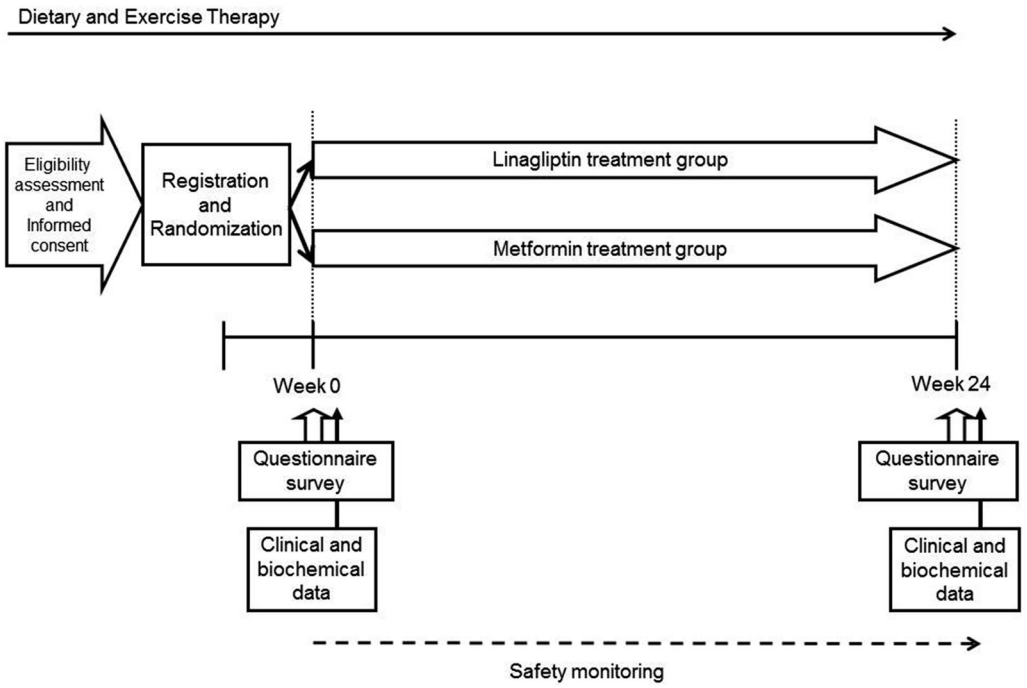

Fig. 1 Flow chart of the study schedule

diarrhea; (9) differences in the proportion of patients with hospitalization for heart failure; and (10) differences in the proportion of other adverse effects.

OHA-Q ver. 2

The OHA-Q ver. 2 is a 23-item, self-administered assessment with three subscales including treatment convenience (9 items; questions 1–9), somatic symptoms (8 items; questions 11–21), and satisfaction (3 items; questions 10, 22, and 23) (Table 2) [20]. The response to each question is scored using a four-point Likert-type scale that ranged from 1 to 4 points. Answers are converted to scores of 0–3. Subscale scores are calculated by summing the response to the items in each subscale. Higher scores represent higher satisfaction.

DTR-QOL Questionnaire

The DTR-QOL is a 29-item, self-administered assessment with four primary scales including burden on social activities and daily activities (13 items), anxiety and dissatisfaction with treatment (8 items), hypoglycemia (4 items), and satisfaction with treatment (4 items) (Table 3) [19]. The DTR-QOL can evaluate the effect of diabetes treatment on patient QOL with high reliability and validity [19]. The response to each question is scored using a seven-point Likert-type scale that ranges from 1 (strongly agree) to 7 (strongly disagree). The scale for items 26–29 is reversed, so that 7 represent the highest QOL score. Domain scores are calculated by summing the response to the items in each domain. Scores are then converted to a range of 0–100. Higher scores represent higher QOL. In each domain, average scores are calculated.

Sample Size

The sample size was not calculated on the basis of scientific evidence because this was an exploratory study. Assuming a treatment dropout rate of 10%, the target number of enrolled patients was set at 22 subjects per group, or 44 subjects in total.

Table 2 Oral Hypoglycemic Agent Questionnaire, version 2 questionnaire and subscale structure

Q1. Do you ever forget to take your diabetes medication? (How many times a week?)
Q2. Are you concerned about the size of the tablets, difficulty swallowing the tablets, etc., when taking diabetes medication?
Q3. Is handling/carrying/preparing to taking diabetes medicine troublesome?
Q4. Are you concerned about being seen by others when taking diabetes medication outside of your home?
Q5. Is it a burden to eat meals at regular times in order to take diabetes medication?
Q6. Is being punctual in taking your diabetes medication and your meals troublesome?
Q7. Is it a burden to take diabetes medication at predetermined times?
Q8. Is the dosing frequency for diabetes medication a hassle?
Q9. Is it difficult to take diabetes medication outside of your home?
Q10. Do you want to continue to take your current diabetes medication?
Q11. Are you concerned about passing gas or rumbling in your stomach?
Q12. Are you concerned about diarrhea?
Q13. Are you concerned about constipation?
Q14. Are you concerned about weight gain?
Q15. Are you concerned about readily becoming hungry?
Q16. Are you concerned about having an upset stomach?
Q17. Are you concerned about swelling of your body?
Q18. Are you worried about hypoglycemia?
Q19. Are you concerned about frequent urination?
Q20. Are you concerned about thirsty?
Q21. Are you concerned about discomfort with urination or genital pruritus?
Q22. Are you satisfied with your current blood glucose control?
Q23. Are you satisfied with your current treatment with the diabetes medication?

The question numbers in the Oral Hypoglycemic Agent Questionnaire, version 2 questionnaire are used in this table

Safety Evaluation

All adverse effects (AEs) during the study are documented to ensure patient safety. AEs are defined as any untoward medical occurrence in a clinical trial subject who has received a medicinal product. AEs do not necessarily have a causal relationship with treatment. The association between AEs and the study medication is classified as either being associated with or not associated with the study drug by one of the investigators. All associated AEs that result in the withdrawal of a subject from the study are monitored until resolution. Serious AEs are defined as death or life-threatening events that required hospitalization, prolonged existing hospitalization, or resulted in persistent or significant disability or incapacity that requires intervention to prevent permanent impairment or damage.

Table 3 Diabetes Therapy-Related QOL questionnaire and domain structure

Domain 1: Burden on social activities and daily activities
Q1. My current diabetes treatment interferes with my work and activities
Q2. My current diabetes treatment limits the scope of my activities
Q3. It is difficult to find places on time for my current diabetes treatment
Q4. My current diabetes treatment interferes with group activities and personal friendships
Q5. It is a burden getting up at a certain time every morning for my current diabetes treatment
Q6. With my current diabetes treatment, the restricted meal times are a burden
Q7. When I eat out, it is difficult to manage my current diabetes treatment
Q8. I feel like my current diabetes treatment takes away the enjoyment of eating
Q9. With my current diabetes treatment, it is hard to curb my appetite
Q10. The time and effort to manage my current diabetes treatment are a burden
Q11. I am constantly concerned about time to manage my current diabetes treatment
Q12. Pain due to my current diabetes treatment is uncomfortable
Q13. Gastrointestinal symptoms (nausea, passing gas, diarrhea, abdominal pain) due to my current diabetes treatment are uncomfortable
Domain 2: Anxiety and dissatisfaction with treatment
Q14. I am bothered by weight gain with my current diabetes treatment
Q19. I have uncomfortable symptoms due to hyperglycemia (high blood glucose)
Q20. I am worried about high blood glucose
Q21. I am dissatisfied that my blood glucose is unstable (high and low)
Q22. I am worried that complications might worse with my current diabetes treatment
Q23. I got anxious thinking about living while on my current diabetes treatment
Q24. I find it unbearable to think that even if I continue my current diabetes treatment, my diabetes may not be cured
Q25. I am concerned that if I continue my current diabetes treatment, the efficacy (effectiveness) may diminish
Domain 3: Hypoglycemia
Q15. I worry about low blood glucose due to my current diabetes treatment
Q16. I am scared because of low blood glucose
Q17. I am sometimes bothered by low blood glucose
Q18. Symptoms due to low blood glucose are uncomfortable
Domain 4: Satisfaction with treatment
Q26. Overall, I am satisfied with my current blood sugar control (glycemic control)
Q27. With my current diabetes treatment, I am confident that I can maintain good blood glucose control
Q28. I am hopeful about the future with my current diabetes treatment
Q29. With regard to diabetes treatment, I am satisfied with current treatment methods

The question numbers in the Diabetes Therapy-Related-QOL questionnaire are used in this table

Statistical Analysis

Efficacy will be analyzed using the full analysis data set, except for the safety analysis. To compare the total OHA-Q ver. 2 score and each OHA-Q ver. 2 domain score between the two treatment groups at the end of the study, statistical analysis will include Student's *t* test and analysis of covariance (ANCOVA) models that include treatment group as a fixed effect and the allocation factors of age (< 65 or ≥ 65 years) and gender (male or female) as covariates. To compare the changes in total and domain DTR-QOL scores, HbA1c, and fasting blood glucose between the two treatment groups at the end of the study, statistical analysis will include Student's *t* test and ANCOVA models that include treatment group as fixed effects and (1) each baseline value as a covariate, (2) allocation factors as covariates, and (3) each baseline value and allocation factors as covariates. For the other variables, comparisons between the groups will be assessed using Student's *t* test or the Wilcoxon rank-sum test for continuous variables, and the chi-square test or Fisher's exact test for categorical variables. Changes from baseline to week 24 within a treatment group will be assessed with the one-sample *t* test or Wilcoxon signed-rank test. The correlation between total OHA-Q ver. 2 score at the end of study or change in DTR-QOL score from baseline to 24 weeks will be evaluated using Pearson's and Spearman's correlation coefficients. All statistical tests will be two-sided with a significance level of 5%. All analyses will be performed using SAS software, version 9.4 (SAS Institute, Cary, NC). The statistical analysis plan will be written by an independent statistician.

Strengths and Limitations of Study Protocol

The strength is a prospective, randomized, open-label, multicenter, parallel-group, comparative trial design. In addition, two questionnaires for evaluating QOL used in this study are valid. On the other hand, the limitations are the small number of participants and the open-label, exploratory trial design.

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Compliance with Ethics Guidelines. The protocol has been approved by the institutional review board of each participating institution in compliance with the Declaration of Helsinki and current legal regulations in Japan. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

Data Availability. The analyzed data sets are available from the corresponding author on reasonable request.

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