Current Medical Research and Opinion

ISSN: 0300-7995 (Print) 1473-4877 (Online) Journal homepage: https://www.tandfonline.com/loi/icmo20

Treatment preference for weekly versus daily DPP-4 inhibitors in patients with type 2 diabetes mellitus: outcomes from the TRINITY trial

Shu Meguro, Shingo Matsui & Hiroshi Itoh

To cite this article: Shu Meguro, Shingo Matsui & Hiroshi Itoh (2019) Treatment preference for weekly versus daily DPP-4 inhibitors in patients with type 2 diabetes mellitus: outcomes from the TRINITY trial, Current Medical Research and Opinion, 35:12, 2071-2078, DOI: 10.1080/03007995.2019.1651130

To link to this article: https://doi.org/10.1080/03007995.2019.1651130

Published online: 22 Aug 2019.

CURRENT MEDICAL RESEARCH AND OPINION
2019, VOL. 35, NO. 12, 2071–2078
https://doi.org/10.1080/03007995.2019.1651130
Article ST-0150.R1/1651130

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Treatment preference for weekly versus daily DPP-4 inhibitors in patients with type 2 diabetes mellitus: outcomes from the TRINITY trial

Shu Meguro[a], Shingo Matsui[b] and Hiroshi Itoh[a]

[a]Department of Nephrology, Endocrinology and Metabolism, Keio University School of Medicine, Tokyo, Japan; [b]Japan Medical Affairs, Takeda Pharmaceutical Company Limited, Tokyo, Japan

ABSTRACT

Objective: To examine patient preference for treatment with the oral once-weekly dipeptidyl peptidase-4 inhibitor (DPP-4i), trelagliptin, and oral once-daily DPP-4i, alogliptin, administered for 8 weeks each in patients with type 2 diabetes mellitus prescribed a daily DPP-4i.

Methods: In this randomized, open-label, two-way crossover study, patients received trelagliptin followed by alogliptin (T-A group) or alogliptin followed by trelagliptin (A-T group), for 8 weeks each (NCT03231709, JapicCTI-173662). Treatment preference was assessed using a standardized questionnaire in the overall population and by baseline characteristics. Other outcomes included patient satisfaction with diabetes treatment (assessed using the Diabetes Treatment Satisfaction Questionnaire [DTSQ]), hemoglobin A1c (HbA1c) levels after 8 weeks of treatment with each agent, and safety.

Results: Sixty patients from two clinical sites were randomized 1:1 to T-A and A-T groups (each $n = 30$); baseline characteristics were similar between groups. After 16 weeks of treatment, 51.7% of patients preferred treatment with alogliptin compared with 30.0% selecting trelagliptin ($p = .014$); preference for alogliptin was consistently greater than for trelagliptin in the secondary analyses by baseline characteristics. DTSQ score and HbA1c levels were similar between treatments after 8 weeks of therapy. Both treatments demonstrated favorable safety and tolerability profiles.

Conclusions: Patients expressed a significantly greater treatment preference for once-daily alogliptin than once-weekly trelagliptin, although patient satisfaction and HbA1c levels were similar across treatments. The decision to administer a once-weekly or once-daily DPP-4i is likely to depend on patient preference, patient-physician discussions, and treatment practices of the prescribing physician.

ARTICLE HISTORY
Received 26 March 2019
Revised 24 July 2019
Accepted 30 July 2019

KEYWORDS
Alogliptin; diabetes mellitus; type 2; patient preference; trelagliptin

Introduction

The primary goal of diabetes treatment is to achieve optimal metabolic control[1]. Suboptimal adherence to antidiabetic treatment can disrupt glucose metabolism[2], thereby increasing the risk of diabetes-related complications. Maintaining good adherence to antidiabetic medications is, therefore, an important factor in achieving glycemic control[2,3].

High frequency of doses, as often as 3-times per day, in the treatment of type 2 diabetes mellitus is associated with poorer compliance to oral antidiabetics when compared with once-daily dosing[4]. The effects of multiple dosing may be exacerbated by the burden of polypharmacy, common among diabetic patients, which can impact patient quality-of-life and further contribute to poor adherence[5]. The results of a study in patients with osteoporosis reported that switching from once-daily bisphosphonates to weekly dosing improved treatment adherence compared with patients who were newly-prescribed a once-weekly regimen[6]. This raises the possibility that a similar reduction in frequency of dosing may improve medication adherence among patients with diabetes.

Trelagliptin is the first once-weekly oral dipeptidyl peptidase-4 (DPP-4) inhibitor, which controls glucose levels by inhibiting DPP-4[7,8]. DPP-4 breaks down glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), both of which have important roles in glucose homeostasis[9]. The inhibition of DPP-4 prolongs the activity of endogenous GLP-1 and GIP, thereby improving glycemic control[10]. Phase 3 findings in patients with type 2 diabetes mellitus demonstrated that less frequent dosing with trelagliptin was non-inferior in reducing hemoglobin A1c (HbA1c) to the once-daily DPP-4 inhibitor, alogliptin, and had a comparable efficacy and safety profile[11]. These results were further supported by a long-term phase 3 study of trelagliptin, as monotherapy or in combination with an existing oral antidiabetic drug, which demonstrated favorable safety and efficacy over 52 weeks[12].

Several published studies have examined patient preferences to weekly DPP-4 inhibitors compared with daily DPP-4 inhibitors. For example, the results of the questionnaire-based study by Suzuki et al.[13] reported that 55.3% of 170

CONTACT Shingo Matsui shingo.matsui@takeda.com Japan Medical Affairs, Takeda Pharmaceutical Company Limited, 1-1, Nihonbashi-Honcho 2-Chome, Chuo-Ku, Tokyo, 103-8668, Japan

patients who took daily DPP-4 inhibitors would be willing to change to a weekly DPP-4 inhibitor. The results of a questionnaire-based study by Higami and Higami[14] reported that 61% of 346 patients with T2DM preferred weekly medication. The results of a study by Uchida[15] reported that 95% of 38 patients showed a preference for once-weekly DPP-4 inhibitors following treatment with once-weekly DPP-4 inhibitors for 3–4 months. Nakamura and Tsukamoto[16] reported that 75.6% of 45 patients preferred treatment with weekly DPP-4 inhibitors 2 months after receiving once-weekly DPP-4 inhibitor trelagliptin. All the above reports suggest that patients have a high interest in once-weekly DPP-4 inhibitors before taking the medication and a high preference after the prescription of such. However, these studies cannot rule out the possible influence of the proximate medication or accustomed drug-taking behavior on preference for the subsequent treatment. This phase 4 study, treatment preference for weekly DPP-4 inhibitors vs daily DPP-4 inhibitors in patients with type 2 diabetes mellitus (TRINITY), aimed to assess whether patients with type 2 diabetes mellitus prefer a once-weekly or once-daily DPP-4 inhibitor, by administering once-daily doses of alogliptin for 8 weeks followed by once-weekly doses of trelagliptin for 8 weeks, or vice versa, for a total duration of 16 weeks.

Methods

Study design

This was a randomized, open-label, two-way crossover study that was designed to assess patient preference for treatment with the once-weekly DPP-4 inhibitor, trelagliptin, or the once-daily DPP-4 inhibitor, alogliptin, in patients with type 2 diabetes mellitus who were already receiving a once-daily DPP-4 inhibitor for at least 8 weeks prior to the start of the study. The study was conducted at two clinical trial hospitals, ToCROM (Tokyo, Japan) and OCROM (Osaka, Japan).

After providing informed consent (week 0), eligible patients were randomized to receive either trelagliptin 100 mg once-weekly for 8 weeks followed by alogliptin 25 mg once a day for 8 weeks (T-A group), or alogliptin followed by trelagliptin (A-T group; same dosing schedules in reverse). The total duration of the study was 16 weeks, with three scheduled visits: at the start of study drug administration (visit 1: week 0); at the switch of study drug (visit 2: week 8); and at the end of the study (visit 3: week 16). Addition of drugs or changes in the dose/regimen of drugs used to treat type 2 diabetes mellitus or concurrent medical conditions, such as hypertension, were not permitted. The study is registered at ClinicalTrials.gov (NCT03231709) and JAPIC (JapicCTI-173662).

Study population

The study recruited adult patients aged $\geq$20 years with a diagnosis of type 2 diabetes mellitus. All patients were required to have an HbA1c value (National Glycohemoglobin Standardization Program [NGSP] value) of $<$10% within 8 weeks prior to the start of the study and an answer to the Diabetes Treatment Satisfaction Questionnaire (DTSQ)[17] at the first study visit (week 0). Patients must have been treated with any of the following once-daily DPP-4 inhibitors for at least 8 weeks prior to the first visit: sitagliptin 50 mg, alogliptin 25 mg, linagliptin 5 mg, teneligliptin 20 mg, or saxagliptin 5 mg. They also had to be able to change treatment from their once-daily DPP-4 inhibitor to once-weekly trelagliptin 100 mg or once-daily alogliptin 25 mg. The main exclusion criteria were: a history of taking the once-weekly DPP-4 inhibitor(s), trelagliptin or omarigliptin; treatment with drugs (other than those for daily oral dosing) used to manage a chronic complication; treatment with the twice-daily DPP-4 inhibitors, vildagliptin or anagliptin, or treatment with an antidiabetic fixed-dose combination pill containing a DPP-4 inhibitor; moderate or severe renal impairment; severe ketosis, diabetic coma or precoma, type 1 diabetes mellitus, severe infection, or serious trauma (before or after surgery) that warranted insulin therapy for glycemic control; a history of hypersensitivity or allergy to DPP-4 inhibitors; serious heart disease, cerebrovascular disorder, or other serious disease; malignancy; or unstable proliferative diabetic retinopathy.

Assessments

Patient preference was assessed at week 16 using a standardized, self-administered, single-item questionnaire for treatment preference, delivered in Japanese. Treatment satisfaction was evaluated at each visit using the Japanese translation of the 8-item DTSQ[17]. Glycemic control was monitored by measuring HbA1c at each visit. Safety was assessed throughout the study by recording adverse events (AEs). AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0.

Study endpoints

The primary endpoint of the study was to assess treatment preference (treatment selection rate) at week 16 based on a patient's answer to the single question in the standardized patient preference questionnaire: "Regarding drug therapy at the end of this study, which treatment would you select from the following choices (from 1 to 4): 1. Either a once-weekly DPP-4 inhibitor or a daily DPP-4 inhibitor; 2. A once-weekly DPP-4 inhibitor; 3. A daily DPP-4 inhibitor; 4. Neither a once-weekly DPP-4 inhibitor nor a daily DPP-4 inhibitor".

Assessment of treatment preference at week 16 by patient demographics and other baseline characteristics was a secondary endpoint. Additional endpoints were change from baseline in DTSQ total score and HbA1c levels at 8 weeks of treatment, treatment compliance, and safety.

Treatment compliance

Treatment compliance by the patient was evaluated by the investigator at each visit based on the following four categories: took the drug the majority of the time (compliance rate

≥90%); usually took the drug (compliance rate 70–89%); took the drug more than half of the time of dosing (compliance rate 50–69%); took the drug less than half of the time of dosing (compliance rate <50%).

Statistical analysis

Planned enrolment for the study was 60 patients (30 patients in each group). Based on the results of the questionnaire for the treatment selection rate after receiving a once-weekly DPP-4 inhibitor[16], treatment selection rates for once-weekly and daily dosing were assumed to be 60% and 20%, respectively, with 20% of patients having no preference. A total of 54 patients were deemed necessary to ensure 90% power in the binomial test with a two-sided significance level at 5%. Assuming a discontinuation rate of 10%, the required number of randomized patients was set at 30 patients per treatment group. With the estimated rate of discontinuation at 10%, the number of randomized patients was set to be 30 patients per group. Two primary analysis sets, the "full analysis set" (FAS) and the "safety analysis set" (SAS) were used in this study. The two primary analysis sets were defined as all enrolled patients who received either study drug at least once during the study after randomization. In addition, patient preference was assessed in patients who received at least one dose of both study drugs.

Treatment preference rates were calculated based on responses to the standardized patient preference questionnaire at the end of treatment (week 16), in each group and both groups combined. Treatment selection rates for the once-weekly or once-daily DPP-4 inhibitor were compared by applying the Mainland–Gart test. For the secondary analysis, treatment preference rates were stratified by baseline factor and were calculated based on responses to the standardized patient preference questionnaire at the end of treatment (week 16), in each group and both groups combined.

DTSQ total score, HbA1c levels, and AEs are reported using summary statistics. DTSQ total score for treatment satisfaction was calculated by summing the points for questions 1, 4, 5, 6, 7, and 8. AEs are reported according to the treatment received at the time of the event.

Statement of ethics

The study protocol was designed in accordance with the principles of the revised Declaration of Helsinki, Ethical Guideline for Clinical Research (Japanese Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health, Labour and Welfare, December 22, 2014), International Conference on Harmonization Guideline for Good Clinical Practice, and applicable regional requirements. The protocol, informed consent, and other information requiring prior approval were reviewed and approved by the internal review board at the study sites. The institutional review board was Medical Corporation Heishinkai OPHAC Hospital. The approval number was 470 CLI. All patients provided written informed consent to participate in the trial. All authors had full access to the data and take responsibility for its integrity and analysis.

Results

Patient disposition

In total, 60 patients were screened for eligibility and signed the informed consent form. All 60 patients deemed eligible for inclusion in the study were randomized 1:1 to either the T-A group ($n = 30$) or the A-T group ($n = 30$). Patient disposition is presented in Figure 1. Two patients in the A-T group discontinued: one due to a pre-treatment event/AE during the trelagliptin period and one due to other reasons during the alogliptin period.

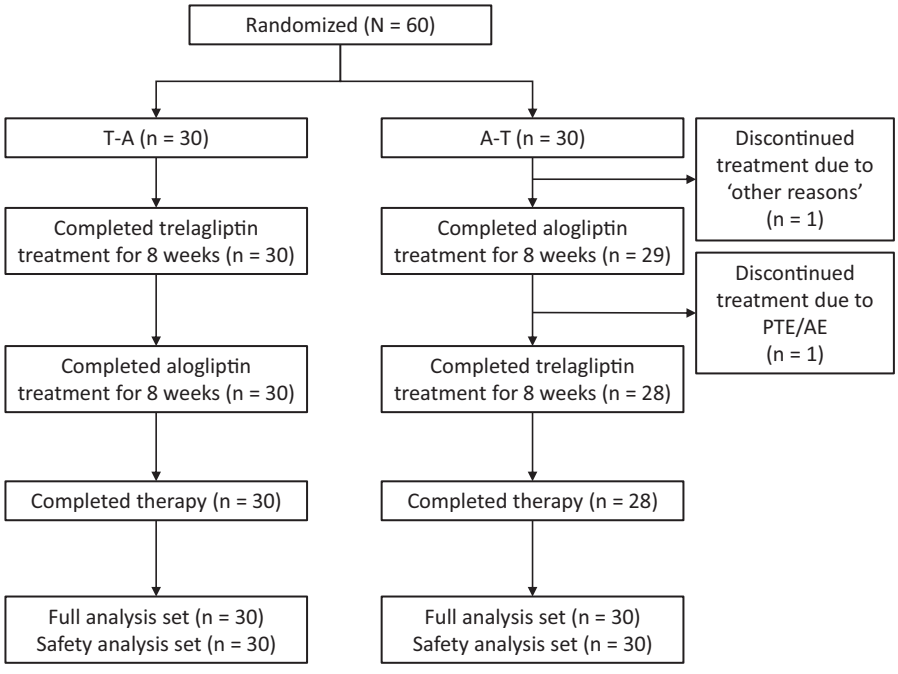

Figure 1. Patient disposition. Abbreviations. A, Alogliptin; AE, Adverse event; PTE, Pre-treatment event; T, Trelagliptin.

Table 1. Demographic and baseline characteristics (FAS).

	Treatment		
	T-A ($n = 30$)	A-T ($n = 30$)	Total ($n = 60$)
Age, years			
Mean (SD)	60.6 (8.86)	59.7 (8.73)	60.1 (8.73)
Age category, *n* (%)			
<65 years	18 (60.0)	20 (66.7)	38 (63.3)
Gender, *n* (%)			
Male	26 (86.7)	28 (93.3)	54 (90.0)
BMI, kg/m^2			
Mean (SD)	24.61 (3.22)	24.19 (3.31)	24.40 (3.24)
Smoker, *n* (%)			
No	27 (90.0)	23 (76.7)	50 (83.3)
Duration of diabetes mellitus, *n* (%)			
≥3 years	26 (86.7)	29 (96.7)	55 (91.7)
<3 years	4 (13.3)	1 (3.3)	5 (8.3)
HbA1c (NGSP), %			
Mean (SD)	7.34 (0.63)	7.41 (0.84)	7.38 (0.74)
DTSQ total score (excluding Q2 and Q3)			
Mean (SD)	23.7 (5.86)	23.0 (5.48)	23.3 (5.64)
Compliance with DPP-4 inhibitors during 4-week period before start of treatment, *n* (%)			
≥90%	30 (100.0)	30 (100.0)	30 (100.0)
Number of oral drugs/day at start of treatment, excluding study drug, *n* (%)			
1–2 tablets	12 (40.0)	9 (30.0)	21 (35.0)
3–5 tablets	13 (43.3)	11 (36.7)	24 (40.0)
≥6 tablets	5 (16.7)	10 (33.3)	15 (25.0)
Presence of metabolic syndrome, *n* (%)			
Yes	11 (36.7)	11 (36.7)	22 (36.7)
No	19 (63.3)	19 (63.3)	38 (63.3)

Abbreviations. A, Alogliptin; BMI, Body mass index; DPP-4, Dipeptidyl peptidase-4; DTSQ, Diabetes Treatment Satisfaction Questionnaire; FAS, Full analysis set; HbA1c, Hemoglobin A1c; NGSP, National Glycohemoglobin Standardization Program; Q, Question; SD, Standard deviation; T, Trelagliptin.

Table 2. Treatment preference at week 16 in the FAS and among patients who received both trelagliptin and alogliptin at least once.

Patient-expressed treatment preference	Number of patients (%)			Mainland–Gart test[a]
	T-A	A-T	Total	
FAS				
n	30	30	60	
Either T or A	4 (13.3)	7 (23.3)	11 (18.3)	
Trelagliptin	8 (26.7)	10 (33.3)	18 (30.0)	$p = .0141$
Alogliptin	18 (60.0)	13 (43.3)	31 (51.7)	
Neither T nor A	0 (0.0)	0 (0.0)	0 (0.0)	
Patients who received both treatments at least once				
n	30	29	59	
Either T or A	4 (13.3)	7 (24.1)	11 (18.6)	
Trelagliptin	8 (26.7)	10 (34.5)	18 (30.5)	$p = .0231$
Alogliptin	18 (60.0)	12 (41.4)	30 (50.8)	
Neither T nor A	0 (0.0)	0 (0.0)	0 (0.0)	

[a]Only calculated for patients who chose trelagliptin or alogliptin.
Abbreviations. A, Alogliptin; FAS, Full analysis set; T, Trelagliptin.

Patient characteristics

Patient demographics and baseline characteristics are summarized in Table 1. Baseline characteristics were similar in the two treatment groups. Most patients were male ($n = 54$ [90.0%]), with a mean age of 60.1 years (standard deviation [SD] = 8.73 years). Fifty-five patients (91.7%) had type 2 diabetes mellitus for ≥3 years, and baseline DTSQ total scores and HbA1c levels were comparable between the two groups.

Treatment preference

Patient preference for treatment (treatment selection rate) at study end, as assessed via the standardized interview question, in the FAS ($n = 60$) and among patients who received at least one dose of both study drugs ($n = 59$), is shown in Table 2. At 16 weeks, patients in the FAS who expressed some preference for trelagliptin or alogliptin expressed a significantly greater treatment preference for alogliptin than trelagliptin (51.7% vs 30.0%, respectively; $p = .0141$, both groups combined; Table 2). Patients who received at least one dose of both study drugs with some preference for trelagliptin or alogliptin also expressed a significantly greater treatment preference for alogliptin compared with trelagliptin (50.8% vs 30.5%, respectively; $p = .0231$, both groups combined; Table 2). Of note, preference for alogliptin was stronger in patients who were first exposed to trelagliptin and then alogliptin (T-A group; 60% of patients preferred alogliptin, 26.7% of patients preferred trelagliptin, and 13.3%

Table 3. Treatment preference at week 16 by demographic and baseline characteristics (FAS).

	Number of patients (%) ($n = 60$)							
	Sub-group, *n*	Either T or A		Trelagliptin		Alogliptin		Neither T nor A	
Age, years, *n* (%)									
Min–<65	38	9	(23.7)	13	(34.2)	16	(42.1)	0	(0.0)
65–<75	22	2	(9.1)	5	(22.7)	15	(68.2)	0	(0.0)
75–≤Max	0	0	—	0	—	0	—	0	—
Gender, *n* (%)									
Male	54	11	(20.4)	16	(29.6)	27	(50.0)	0	(0.0)
Female	6	0	(0.0)	2	(33.3)	4	(66.7)	0	(0.0)
BMI, kg/m^2, *n* (%)									
Min–<18.5	1	0	(0.0)	1	(100.0)	0	(0.0)	0	(0.0)
18.5–<25.0	36	9	(25.0)	9	(25.0)	18	(50.0)	0	(0.0)
25.0–≤Max	23	2	(8.7)	8	(34.8)	13	(56.5)	0	(0.0)
Duration of diabetes mellitus, *n* (%)									
≥3 years	55	10	(18.2)	17	(30.9)	28	(50.9)	0	(0.0)
<3 years	5	1	(20.0)	1	(20.0)	3	(60.0)	0	(0.0)
Work status, *n* (%)									
Working	47	9	(19.1)	16	(34.0)	22	(46.8)	0	(0.0)
Unemployed	13	2	(15.4)	2	(15.4)	9	(69.2)	0	(0.0)
Alcohol intake history, *n* (%)									
Regular drinker	35	5	(14.3)	7	(20.0)	23	(65.7)	0	(0.0)
Occasional drinker	5	2	(40.0)	3	(60.0)	0	(0.0)	0	(0.0)
Non-drinker	20	4	(20.0)	8	(40.0)	8	(40.0)	0	(0.0)
Smoker, *n* (%)									
Yes	10	4	(40.0)	4	(40.0)	2	(20.0)	0	(0.0)
No	50	7	(14.0)	14	(28.0)	29	(58.0)	0	(0.0)
Experience of educational hospitalization on diabetes,[a] *n* (%)									
Yes	5	3	(60.0)	0	(0.0)	2	(40.0)	0	(0.0)
No	55	8	(14.5)	18	(32.7)	29	(52.7)	0	(0.0)
Living status, *n* (%)									
Live alone	8	1	(12.5)	3	(37.5)	4	(50.0)	0	(0.0)
Live with someone else	52	10	(19.2)	15	(28.8)	27	(51.9)	0	(0.0)
Compliance with DPP-4 inhibitors during 4-week period before start of treatment, *n* (%)									
≥90%	60	11	(18.3)	18	(30.0)	31	(51.7)	0	(0.0)
Number of oral drugs/day at start of treatment,[b] *n* (%)									
1–2 tablet(s)	21	1	(4.8)	7	(33.3)	13	(61.9)	0	(0.0)
3–5 tablets	24	5	(20.8)	8	(33.3)	11	(45.8)	0	(0.0)
≥6 tablets	15	5	(33.3)	3	(20.0)	7	(46.7)	0	(0.0)
Presence of metabolic syndrome, *n* (%)									
Yes	22	4	(18.2)	4	(18.2)	14	(63.6)	0	(0.0)
No	38	7	(18.4)	14	(36.8)	17	(44.7)	0	(0.0)
HbA1c (NGSP), *n* (%)									
<7.0%	18	1	(5.6)	6	(33.3)	11	(61.1)	0	(0.0)
7.0–<8.0%	29	7	(24.1)	8	(27.6)	14	(48.3)	0	(0.0)
≥8.0%	13	3	(23.1)	4	(30.8)	6	(46.2)	0	(0.0)

[a]Some patients had taken part in an educational hospitalization program to educate them on interventions such as insulin injections and diet therapy.
[b]Excluding study drugs.
Abbreviations. A, Alogliptin; BMI, Body mass index; DPP-4, Dipeptidyl peptidase-4; FAS, Full analysis set; HbA1c, Hemoglobin A1c; NGSP, National Glycohemoglobin Standardization Program; T, Trelagliptin.

Table 4. DTSQ total score and HbA1c at 8 weeks after the start of administration of each study drug.

	Baseline	8 weeks after start of administration	
	Total ($n = 60$)	Trelagliptin ($n = 59$)	Alogliptin ($n = 59$)
DTSQ total score			
Mean (SD)	23.3 (5.64)	25.2 (6.10)	25.1 (6.30)
HbA1c, %			
Mean (SD)	7.38 (0.739)	7.47 (0.773)	7.45 (0.814)

Abbreviations. DTSQ, Diabetes Treatment Satisfaction Questionnaire; HbA1c, Hemoglobin A1c; SD, Standard deviation.

of patients stated no preference) than in patients who were first exposed to alogliptin and then trelagliptin (A-T group; 43.3%, and 33.3% of patients preferred alogliptin, and trelagliptin, respectively; 23.3% of patients stated no preference; Table 2).

In the secondary analysis, treatment preference by demographic and baseline characteristics showed a greater preference for alogliptin than trelagliptin at 16 weeks except in sub-groups that included one patient, in patients who occasionally consumed alcohol, and smoked. In two sub-groups an equal number of patients preferred alogliptin, and trelagliptin (weight 50– < 60 kg; no consumption of alcohol) (both groups combined; Table 3).

Treatment satisfaction

Patient satisfaction with diabetes treatment, as assessed via the DTSQ after 8 weeks of therapy with each agent, is shown in Table 4. There were similar but small improvements in DTSQ total score from baseline in both treatment groups; Table 4.

HbA1c score

HbA1c values after 8 weeks' therapy with each agent, aggregated across the whole study group and without regard for

Table 5. Overview of treatment-emergent adverse events (SAS).

Patients, *n* (%)	Trelagliptin 100 mg ($n = 59$)[a]	Alogliptin 25 mg ($n = 60$)
Any TEAE	8 (13.6)	4 (6.7)
Mild	8 (13.6)	3 (5.0)
Moderate	1 (1.7)	1 (1.7)
Severe	0 (0.0)	0 (0.0)
Leading to discontinuation	1 (1.7)	0 (0.0)
Drug-related TEAEs	0 (0.0)	0 (0.0)
SAE	1 (1.7)	0 (0.0)
Drug-related SAEs	0 (0.0)	0 (0.0)
SAE leading to discontinuation	1 (1.7)	0 (0.0)
Deaths	0 (0.0)	0 (0.0)

[a]The total number of patients who received trelagliptin was short in the SAS due to one patient discontinuing dosing before treatment period 2 with trelagliptin.
Abbreviations. SAE, Serious adverse event; SAS, Safety analysis set; TEAE, Treatment-emergent adverse event.

the order in which the treatments were received, are shown in Table 4. HbA1c values after 8 weeks of treatment with either agent were comparable and remained similar to baseline values.

Treatment compliance

A total of 57 patients (96.6%) receiving trelagliptin and 58 patients (96.7%) receiving alogliptin demonstrated ≥90% treatment compliance. Two patients (3.4%) receiving trelagliptin and one patient (1.7%) receiving alogliptin demonstrated 70–89% compliance with treatment.

Safety

In total, eight patients (13.6%) receiving trelagliptin and four patients (6.7%) receiving alogliptin experienced a treatment-emergent AE (TEAE) during treatment (Table 5). Most TEAEs were mild in intensity, with no severe events reported; one patient for each treatment experienced an AE of moderate severity. Infections and infestations were the most common TEAE by system organ class, experienced by six patients (10.2%) receiving trelagliptin, which were mild in intensity, and three patients (5.0%) receiving alogliptin, which were mild-to-moderate in intensity. Two patients (3.4%) receiving trelagliptin and one patient (1.7%) receiving alogliptin experienced a viral upper respiratory tract infection, both mild in intensity.

One patient (1.7%) receiving trelagliptin experienced two serious AEs that led to trelagliptin discontinuation, with examination revealing colon cancer as the reason for both events. There were no drug-related TEAEs, and no deaths were reported during the study.

Discussion

The increasing prevalence of diabetes in the global and Japanese populations[18,19] coupled with the availability of numerous treatment options, necessitate identification of patient treatment preferences, as this plays a major part in adherence to therapy and subsequent efficacy. In this study, we showed that patients, independent of their baseline characteristics or demographics, expressed a significantly greater treatment preference for once-daily alogliptin than once-weekly trelagliptin. Patients had similar improvements from baseline in DTSQ total score and stable HbA1c levels after 8 weeks of either treatment. Both treatments had favorable safety and tolerability profiles, with no new safety signals identified.

Barriers to treatment adherence in patients with type 2 diabetes mellitus may include patient factors, regimen complexity or dosing frequency, and factors such as inadequate follow-up or support[20,21]. In contrast to the results of our current study, recent questionnaire-based studies have reported patient preference for weekly rather than daily DPP-4 inhibitors[14,15]. The results of one such study reported that 55.3% of 170 patients taking daily DPP-4 inhibitors would prefer to change to a weekly DPP-4 inhibitor[13]. Similarly, Nakamura and Tsukamoto[16] reported that 75.6% of 45 patients selected weekly DPP-4 inhibitors as their preferred treatment 2 months after receiving once-weekly DPP-4 inhibitor trelagliptin. While these studies suggest patient preference for once-weekly DPP-4 inhibitors, they cannot rule out the possible influence exerted by other prescribed medications and individual habitual drug-taking behavior for any subsequent treatment. Research for other chronic conditions has also shown that weekly treatment is preferred to daily treatment, contrary to the findings reported in this study. For example, in a randomized, open-label, multi-center crossover study of 406 post-menopausal women with osteoporosis, 84% expressed a preference for once-weekly vs once-daily dosing[22].

The outcomes of this study suggest that patients did not feel inconvenienced by taking a once-daily DPP-4 inhibitor in addition to their existing medications. However, it should be noted that patients enrolled in this study were already receiving a once-daily DPP-4 inhibitor, and all of them showed relatively stable glycemic control as a requirement of the eligibility criteria. This could mean that these patients were already using once-daily DPP-4 inhibitors routinely and effectively, which may have influenced patient preference for treatment, resulting in biased preference for continued use of once-daily alogliptin. Another possible reason that patients preferred once-daily alogliptin to once-weekly trelagliptin could be the higher incidence of AEs in patients receiving weekly trelagliptin (13.6%) vs those receiving weekly alogliptin (6.7%) in this study. However, as overall incidence was low overall for both groups, and most events were mild in intensity, it is unlikely that this would have had

a strong influence on drug preference in this instance. Nonetheless, it would be interesting to understand how these factors may have influenced the results. Unfortunately, our analysis is limited in this regard, as we did not collect qualitative data from patients on reasons for treatment preference. Interestingly, patient preference for daily alogliptin over weekly trelagliptin was more pronounced in those who received trelagliptin first (T-A group) vs those who received alogliptin first (A-T group). Given the similar efficacy (based on measurement of HbA1c levels) and treatment satisfaction (based on assessment of DTSQ total score) between once-weekly trelagliptin and once-daily alogliptin, the choice between the two agents remains dependent on patient preference and lifestyle, as well as the clinical practices and experience of the treating physician.

The proportion of patients who preferred a once-weekly DPP-4 inhibitor in our study was ~30%. This is in contrast to a retrospective analysis of administrative claims data collected in the Medical Data Vision (MDV) database between the launch of trelagliptin in May 2015 and June 2016, in which the use of once-weekly DPP-4 inhibitors among Japanese patients with type 2 diabetes was below 1%[23]. The data analyzed in the MDV database was obtained immediately after the launch of trelagliptin. Based on the authors' experience and medication usage data from pharmaceutical companies in Japan in 2017 and 2018, it is inferred that the prescription of once-weekly DPP-4 inhibitors including trelagliptin is still low at ~2%. This deviation between the usage and patient preference of once-weekly DPP-4 inhibitors may be due to a lack of communication between the doctor and the patient in clinical practice, or to "clinical inertia"[24]. In any case, good communication and better education on available treatment options are critical in making appropriate treatment choices, while paying attention to patient preference.

The main limitation of the study was the small number of patients enrolled, all of which had been previously treated with any of the following once-daily DPP-4 inhibitors for at least 8 weeks prior to the first visit: sitagliptin 50 mg, alogliptin 25 mg, linagliptin 5 mg, teneligliptin 20 mg, or saxagliptin 5 mg. Additional studies utilizing larger patient populations and longer treatment periods may be warranted to provide greater insight into treatment preferences and satisfaction for trelagliptin and alogliptin in patients with type 2 diabetes mellitus. Additionally, further studies should include more female patients, as the patient population in this study was predominantly male (90.0%), meaning that the findings cannot be generalized to female patients. The two participating clinical sites in Japan are known as clinical trial hospitals. Patients attending the hospitals already had an interest in participating in a clinical trial and thus disclosed their medical records for screening and eligibility. For these reasons, informed consent was obtained from all 60 patients who were already considered eligible. Lastly, as this study was performed in a clinical trial/research setting, patients may have been more compliant than in a real-world situation, and the results may not be directly representative of patient real-world experience.

Conclusions

At the end of the 16-week study, patients expressed a significantly greater treatment preference for once-daily alogliptin 25 mg over once-weekly trelagliptin 100 mg. Treatment satisfaction and glycemic control with the two therapies were similar. Trelagliptin 100 mg and alogliptin 25 mg were well tolerated and no new safety signals were identified. The decision to administer once-weekly or once-daily DPP-4 inhibitor treatment is likely to depend on patient preference, patient–physician discussions, and the preferences and clinical practices of the treating physician.

Transparency

Declaration of funding

Funding for this research was provided by Takeda Pharmaceutical Company Limited, Tokyo, Japan.

Author contributions

Shu Meguro and Hiroshi Itoh: Conception and design of the study, analysis and interpretation of data, drafting and critically revising the manuscript, and providing final approval of the version to be published. Shingo Matsui: Analysis and interpretation of data, drafting and critically revising the manuscript, and providing final approval of the version to be published.

Declaration of financial/other relationships

Shu Meguro has participated in Speakers Bureau for Takeda Pharmaceutical Co. Ltd., and Nippon Boehringer Ingelheim Co., Ltd.; Shingo Matsui is a full time employee of Takeda Pharmaceutical Company Limited; Hiroshi Itoh has received grants/research from Takeda Pharmaceutical Co. Ltd., Shionogi & Co., Ltd., Eli Lilly Japan K.K., Novartis Pharma K.K., Teijin Pharma Ltd., Chugai Pharmaceutical Co., Ltd., Kyowa Hakko Kirin Co., Ltd., Astellas Pharma Inc., Daiichi Sankyo Co., and Sumitomo Dainippon Pharma Co., Ltd., has provided consultant/advisor services for Nipro Corporation, and SBI Pharmaceuticals Co., Ltd., and participated in Speakers Bureau for Takeda Pharmaceutical Co. Ltd., Mitsubishi Tanabe Pharma Corporation MSD K.K., and Nippon Boehringer Ingelheim Co., Ltd. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Acknowledgements

We acknowledge Dr Hisayoshi Daito, OCROM Clinic, Osaka, Japan, and Dr Osamu Matsuoka, ToCROM Clinic, Tokyo, Japan for their contribution in the conduct of this study. The authors would also like to acknowledge Professor Clare Bradley and Health Psychology Research Limited as the owners of the DTSQ questionnaire and to thank them for permitting its use in this trial. We acknowledge Hashem Dbouk and Sabah Farooq of FireKite, an Ashfield company, part of UDG Healthcare plc, for writing support during the development of this manuscript, which was funded by Takeda Pharmaceutical Co. Ltd. (Tokyo, Japan), and complied with Good Publication Practice 3 ethical guidelines (Battisti et al., *Ann Intern Med*. 2015;163:461–464).

Availability of data and material

Takeda makes patient-level, de-identified data sets and associated documents available after applicable marketing approvals and commercial availability have been received, an opportunity for the primary

publication of the research has been allowed, and other criteria have been met as set forth in Takeda's Data Sharing Policy (see https://www.takedaclinicaltrials.com/ for details). To obtain access, researchers must submit a legitimate academic research proposal for adjudication by an independent review panel, who will review the scientific merit of the research and the requestor's qualifications and conflict of interest that can result in potential bias. Once approved, qualified researchers who sign a data sharing agreement are provided access to these data in a secure research environment.

References

[1] Suh S, Kim JH. Glycemic variability: how do we measure it and why is it important? Diabetes Metab J. 2015;39:273–282.

[2] Farmer AJ, Rodgers LR, Lonergan M, et al. Adherence to oral glucose-lowering therapies and associations with 1-year HbA1c: a retrospective cohort analysis in a large primary care database. Diabetes Care. 2016;39:258–263.

[3] Krapek K, King K, Warren SS, et al. Medication adherence and associated hemoglobin A1c in type 2 diabetes. Ann Pharmacother. 2004;38:1357–1362.

[4] Paes AH, Bakker A, Soe-Agnie CJ. Impact of dosage frequency on patient compliance. Diabetes Care. 1997;20:1512–1517.

[5] Murray MD, Kroenke K. Polypharmacy and medication adherence: small steps on a long road. J Gen Intern Med. 2001;16:137–139.

[6] Tanaka R, Hayakawa K, Oshima H. Drug compliance of bisphosphonate in Japan: cohort study of bisphosphonate in a private clinic [in Japanese]. Osteoporosis Japan. 2009;17:252–255.

[7] Takeda Pharmaceutical Company Limited. Report on the deliberation results. 2015. [cited 2018 November 13]; Available from: https://www.pmda.go.jp/files/000213963.pdf

[8] Grimshaw CE, Jennings A, Kamran R, et al. Trelagliptin (SYR-472, Zafatek), novel once-weekly treatment for type 2 diabetes, inhibits dipeptidyl peptidase-4 (DPP-4) via a non-covalent mechanism. PLoS One. 2016;11:e0157509.

[9] Rohrborn D, Wronkowitz N, Eckel J. DPP4 in Diabetes. Front Immunol. 2015;6:386.

[10] Patel BD, Ghate MD. Recent approaches to medicinal chemistry and therapeutic potential of dipeptidyl peptidase-4 (DPP-4) inhibitors. Eur J Med Chem. 2014;74:574–605.

[11] Inagaki N, Onouchi H, Maezawa H, et al. Once-weekly trelagliptin versus daily alogliptin in Japanese patients with type 2 diabetes: a randomised, double-blind, phase 3, non-inferiority study. Lancet Diabetes Endocrinol. 2015;3:191–197.

[12] Inagaki N, Sano H, Seki Y, et al. Long-term safety and efficacy of a novel once-weekly oral trelagliptin as monotherapy or in combination with an existing oral antidiabetic drug in patients with type 2 diabetes mellitus: A 52-week open-label, phase 3 study. J Diabetes Investig. 2016;7:718–726.

[13] Suzuki D, Kuroki H, Tsukada A, et al. Do the patients prefer to take once weekly DPP-4 inhibitors? [in Japanese]. Prog Med. 2016;36:389–392.

[14] Higami K, Higami S. Adherence of oral antidiabetic medication and preference of once a week medication: a questionnaire survey to the patients with diabetes [in Japanese]. Prog Med. 2016;36:1415–1419.

[15] Uchida D. DPP-4 inhibitor: efficacy of once weekly drugs and their effective dosing [in Japanese]. Japanese Journal of Diabetes Master Clinician. 2017;15:26–31.

[16] Nakamura T, Tsukamoto K. Survey for once weekly DPP-4 inhibitor trelagliptin [in Japanese]. The 54th Annual Meeting of Japan Diabetes Society. Chugoku Shikoku Regional Association. 2017;60:390–424.

[17] Bradley C. Diabetes treatment satisfaction questionnaire (DTSQ). In: Bradley C, ed. Handbook of psychology and diabetes. Chur, Switzerland: Harwood Academic 1994. 111–132.

[18] IDF Diabetes Atlas. 8th ed. 2017. [cited 2018 November 13]; Available from: http://diabetesatlas.org/resources/2017-atlas.html

[19] Charvat H, Goto A, Goto M, et al. Impact of population aging on trends in diabetes prevalence: a meta-regression analysis of 160,000 Japanese adults. J Diabetes Invest. 2015;6:533–542.

[20] American Diabetes Association. Promoting health and reducing disparities in populations. Diabetes Care. 2017;40:S6–S10.

[21] Garcia-Perez LE, Alvarez M, Dilla T, et al. Adherence to therapies in patients with type 2 diabetes. Diabetes Ther. 2013;4:175–194.

[22] Kendler D, Kung AW, Fuleihan Gel H, et al. Patients with osteoporosis prefer once weekly to once daily dosing with alendronate. Maturitas. 2004;48:243–251.

[23] Sakaguchi K, Oh A, Kisanuki K, et al. Treatment patterns, persistence and adherence rates of DPP-4 inhibitors in patients with type 2 diabetes mellitus in Japan: a claims-based cohort study. Poster presented at 10th Scientific Meeting of the Asian Association for the Study of Diabetes (AASD); 2018. November 22–25; Kuala Lumpur, Malaysia; 2018.

[24] Reach G, Pechtner V, Gentilella R, et al. Clinical inertia and its impact on treatment intensification in people with type 2 diabetes mellitus. Diabetes Metab. 2017;43:501–511.