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BRIEF REPORT

Comparison of tofogliflozin versus glimepiride as the third oral agent added to metformin plus a dipeptidyl peptidase-4 inhibitor in Japanese patients with type 2 diabetes: A randomized, 24-week, open-label, controlled trial (STOP-OB)

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Abstract

Metformin plus a dipeptidyl peptidase-4 inhibitor (DPP-4i) is the most common therapy for Japanese patients with type 2 diabetes. This 24-week, multicentre, open-label, parallel-group trial randomized patients on dual therapy to add-on tofogliflozin (20 mg/day, n = 33) or glimepiride (0.5 mg/day, n = 31). The primary outcome was change in body fat percentage. The secondary outcomes included changes in HbA1c, fat mass, fat-free mass, liver function variables and uric acid. Tofogliflozin and glimepiride reduced HbA1c to a similar extent. Body fat percentage did not change from baseline in either group. Fat mass was reduced by tofogliflozin but was increased by glimepiride (by −2.0 ± 1.7 kg and +1.6 ± 1.6 kg, P = .002). Fat-free mass was also reduced by tofogliflozin and increased by glimepiride (by −1.3 ± 1.3 kg and

+0.9 ± 2.0 kg, $P < .001$). Alanine aminotransferase and uric acid levels were reduced by tofogliflozin ($P = .006$ and $P < .001$, respectively). These data provide novel information useful for selecting the third oral agent for patients whose diabetes is inadequately controlled with metformin plus DPP-4i dual therapy.

KEYWORDS

body composition, clinical trial, DPP-4 inhibitor, SGLT2 inhibitor, sulphonylureas, type 2 diabetes

1 | INTRODUCTION

Japanese patients with type 2 diabetes (T2D) are usually treated, after lifestyle modifications, with biguanides, sulfonylureas (SUs) or a DPP-4 inhibitor (DPP-4i). Metformin plus a DPP-4i is the most common regimen.[1] The previously most popular SUs, or one of the recently developed sodium-glucose co-transporter-2 inhibitor (SGLT2i) class agents, are now widely regarded as appropriate third-line agents. However, a definitive comparison of these drugs is lacking.

The efficacy of SUs for controlling blood glucose is well recognized. Although serious concerns about cardiovascular safety have been discussed,[2] a recent study has suggested that cardiovascular safety should no longer be considered when selecting SUs.[3] SGLT2i agents not only ameliorate glycaemic control but also exert pleiotropic effects on diabetic complications.[4] Tofogliflozin is the SGLT2i with the highest selectivity in this class.[5] Systematic reviews of previous studies have indicated the glycaemic control achieved by triple combination therapies to be similar.[6,7] Thus, benefits other than glycaemic control as well as disadvantages merit consideration.

In this trial, because body fat percentage was shown to be strongly associated with T2D,[8] we evaluated changes in body composition, with body fat percentage being the primary outcome, between patients with either tofogliflozin or glimepiride added to their metformin plus DPP-4i dual therapy regimens.

2 | MATERIALS AND METHODS

2.1 | Trial design

The SGLT2i, TOfogliflozin versus glimepiride, comparative trial in Patients with type 2 diabetes On Body composition (STOP-OB) was a multicentre, randomized, open-label, parallel-group trial. The rationale, design and protocol were previously described.[9] This trial was registered on the University Hospital Medical Information Network (UMIN000026161). The protocol was approved by the institutional review boards of the participating institutions (Table S1) and the trial was conducted in accordance with the Ethical Guidelines published by the Ministry of Health, Labor and Welfare of Japan and the Helsinki Declaration of 1964, as revised in 2013.

Patents with T2D treated with metformin and a DPP-4i were asked to participate in this trial. Additional inclusion criteria were HbA1c levels of >7.0% but ≤9.0% and being aged ≥20 and <75 years. The exclusion criteria were previously described.[9] Using the web-based minimization method for HbA1c and body mass index (BMI), patients were randomized to tofogliflozin (20 mg/day) or glimepiride (0.5 mg/day) and treated for 24 weeks. Investigators were blinded to the sequence allocation. Patients' regimens other than the trial drugs remained unchanged.

2.2 | Planned outcomes and safety evaluation

The primary outcome was the change in body fat percentage. Secondary outcomes were changes in other body composition variables: body weight, BMI and abdominal circumference, as well as blood pressure, glucose metabolism variables, and liver and kidney functions. Body composition variables were measured by the bio-impedance method (BIA), employing a dual-frequency body composition analyser (DC-430A, Tanita, Tokyo, Japan).

Incidences of adverse events were periodically ascertained. Investigators recorded the procedures, outcomes and relationships to the trial drugs in the case report form.

2.3 | Sample size and statistical analysis

A preceding study[10] found that body fat percentage changed in response to 52-week treatments with empagliflozin and glimepiride by −0.6% and 1.1%, respectively. SGLT2i effects on body composition were similar at 24 and 52 weeks in Japanese patients with 2TD.[11] Thus, we estimated changes in body fat percentage after 24-week treatments with tofogliflozin and glimepiride: −0.6% ± 2.2% and 1.1% ± 2.2%, respectively. Based on these estimations and with a two-sided significance level of 5% and power of 80%, the number of patients required to detect a significant difference in body fat percentage change between the two groups was 28 per group. Assuming a 10% drop-out during the trial, we set the target number of patients at 32 per group.

The body fat percentage change was assessed using analysis of covariance models including the treatment group as the fixed effect and baseline HbA1c and BMI as covariances. For the sensitivity

analysis, we applied the mixed effects model for repeated measures. For continuous variables, data were expressed as mean ± standard deviation or the median value with interquartile range. We employed Student's t-test or Wilcoxon signed-rank test for comparisons between groups, and the one-sample t-test for within-group changes. In the analysis of adverse events, Fisher's exact test was applied. The planned analysis was described in detail in the statistical analysis plan.

3 | RESULTS

Sixty-four patients were randomly assigned to receive tofogliflozin or glimepiride and 61 completed the trial (Figure S1). Baseline characteristics were similar in the two groups (Table S2). HbA1c levels were similarly reduced from baseline (7.4% ± 0.5% and 7.5% ± 0.4%) by −0.4% ± 0.8% (P = .017) and −0.6% ± 0.6% (P = .001) in the tofogliflozin and glimepiride groups, respectively.

Body fat percentage at treatment completion, the primary endpoint, showed no change from baseline in either group (Table 1). There was no significant between-group difference (−0.33%, 95% CI [−1.62, 0.96]). Analysis by the mixed effects model for repeated measures yielded similar results.

The secondary body composition outcomes are summarized in Table 2. Body weight was significantly reduced from baseline by 2.0 ± 1.7 kg (P < .001) in the tofogliflozin group, while being increased by 1.6 ± 1.6 kg (P < .001) in the glimepiride group. Fat mass was also reduced by 0.7 ± 1.5 kg (P = .018) and tended to be increased by 0.7 ± 1.8 kg (P = .050), respectively, resulting in a significant between-group difference (P = .002). Respective fat-free masses were reduced and increased (by −1.3 ± 1.3 kg, P < .001 and +0.9 ± 2.0 kg, P = .019). Altered fat-free mass appeared to mainly be attributable to changes in body water contents (by −1.0 ± 1.4 kg, P < .001 and +0.7 ± 1.3 kg, P = .009). In addition, abdominal circumference was decreased from baseline in the tofogliflozin group (P < .001), while being increased in the glimepiride group (P = .013) (Table 2).

Systolic and diastolic blood pressures were below baseline in the tofogliflozin group (Table S3). The between-group differences at 24 weeks were not, however, significant for either systolic (P = .083) or diastolic (P = .112) blood pressure. Alanine aminotransferase and uric acid decreased in the tofogliflozin group, resulting in significant group differences (P = .006 and P < .001, respectively).

Effects of tofogliflozin and glimepiride on islet function were analysed by employing oral glucose tolerance tests at baseline and week 24 (Table S4). Glucose excursions were similarly reduced in the two groups. Insulin secretion was increased in the glimepiride (P = .012) but not in the tofogliflozin group, while fasting glucagon levels were elevated in the tofogliflozin (P = .041) but not in the glimepiride group. The glucagon response was also greater in the tofogliflozin group (P = .017), although the between-group difference was not statistically significant (P = .077).

Adverse events, none severe, were observed in four patients in each group (Table S5). One patient in the glimepiride group experienced hypoglycaemia twice, while none of those given tofogliflozin showed hypoglycaemia.

4 | DISCUSSION

We directly compared tofogliflozin and glimepiride in patients with inadequate control of T2D using metformin plus a DPP-4i. Our study provides novel information useful for selecting the third oral agent to be added to dual therapy.

Several studies have analysed SGLT2i effects on body composition.[10–17] In this trial, body fat percentage did not change in either group, while several studies have shown SGLT2i-induced body fat percentage reductions.[12,13,16] We also found that tofogliflozin

TABLE 1 Effect on body fat percentage

		Mean ± SD (n)			
		Tofogliflozin		Glimepiride	P-value[a]
0 wk		28.5 ± 10.0 (32)		28.8 ± 7.2 (31)	.91
24 wk		28.3 ± 9.3 (33)		28.6 ± 7.7 (29)	.89
Changes		−0.12 ± 1.91 (32)		0.21 ± 2.97 (29)	.60
P-value[b]		.72		.71	
		Adjusted mean changes (SE)			
		Tofogliflozin	Glimepiride	Difference (95% CI) (Tofogliflozin − Glimepiride)	P-value[a]
ANCOVA	Change from baseline (%)	−0.17 (0.48) n = 32	0.16 (0.51) n = 29	−0.33 (−1.62, 0.96)	0.61
MMRM	Change from baseline (%)	−0.11 (0.48) n = 32	0.23 (0.50) n = 30	−0.34 (−1.62, 0.95)	0.60

Data represent mean ± SD (n).

Abbreviations: ANCOVA, analysis of covariance; MMRM, mixed effects model for repeated measures.

[a]Between-group difference.

[b]Difference at 24 weeks from the baseline.

TABLE 2 Effect on body composition, body mass index (BMI) and abdominal circumference

		Tofogliflozin	Glimepiride	*P*-value[a]
Body weight (kg)	0 wk	67.0 ± 12.3 (32)	69.0 ± 12.9 (31)	.531
	24 wk	65.4 ± 11.8 (33)	70.2 ± 13.7 (29)	.141
	Changes	−2.0 ± 1.7 (32)	1.6 ± 1.6 (29)	<.001
	P-value[b]	<.001	<.001	
BMI (kg/m^2)	0 wk	25.3 ± 3.9 (32)	25.4 ± 3.8 (31)	.86
	24 wk	24.6 ± 3.6 (33)	25.8 ± 3.7 (29)	.200
	Changes	−0.8 ± 0.6 (32)	0.5 ± 0.6 (29)	<.001
	P-value[b]	<.001	<.001	
Fat mass (kg)	0 wk	19.4 ± 8.5 (32)	20.0 ± 6.7 (31)	.733
	24 wk	18.8 ± 7.8 (33)	20.3 ± 6.9 (29)	.400
	Changes	−0.7 ± 1.5 (32)	0.7 ± 1.8 (29)	.002
	P-value[b]	.018	.050	
Fat-free mass (kg)	0 wk	47.6 ± 9.5 (32)	49.0 ± 9.5 (31)	.577
	24 wk	46.7 ± 9.1 (33)	49.9 ± 9.9 (29)	.185
	Changes	−1.3 ± 1.3 (32)	0.9 ± 2.0 (29)	<.001
	P-value[b]	<.001	.019	
Total body water (kg)	0 wk	31.5 ± 6.6 (32)	31.5 ± 6.3 (31)	.983
	24 wk	30.8 ± 6.0 (33)	32.1 ± 6.7 (29)	.406
	Changes	−1.0 ± 1.4 (32)	0.7 ± 1.3 (29)	<.001
	P-value[b]	<.001	.009	
Abdominal circumference (cm)	0 wk	88.9 ± 10.1 (32)	90.7 ± 8.6 (30)	.448
	24 wk	86.6 ± 9.4 (33)	92.8 ± 9.1 (29)	0.011
	Changes	−2.7 ± 2.4 (32)	2.5 ± 5.0 (28)	<.001
	P-value[b]	<.001	.013	

Data represent mean ± SD (n).
[a]Between-group difference.
[b]Difference at 24 weeks from the baseline.

reduced both body fat mass and fat-free mass. Although body fat mass was reduced by SGLT2is in all prior studies, the extent of body fat mass reduction appears to be greater in patients with higher basal BMI levels.[10–17] Accordingly, decreases in body fat percentage tend to be observed in studies employing high-BMI cohorts.[12,13,16] No reduction in body fat percentage despite reduced body fat mass appears to be attributable to fat-free mass being reduced in similar proportion in patients treated with tofogliflozin. Our patients had an average body weight of 68 kg and a BMI of 25.4 kg/m^2. Patients with higher initial body weight may experience greater body fat percentage reductions when tofogliflozin is added to dual therapy.

We also found that glimepiride increased not only body weight but also fat mass and fat-free mass. A weight-increasing effect of SUs is a long-term concern, although there are few reports evaluating body compositions in patients treated with SUs.[18] Increased insulin secretion might be related to the increases in these variables observed in this trial.

Interestingly, tofogliflozin increased plasma glucagon levels at 24 weeks. An empagliflozin effect on serum glucagon reportedly disappeared after 4 weeks.[19] This difference might be associated with the background presence or absence of DPP-4is. Tofogliflozin reduced alanine aminotransferase and uric acid levels as well as systolic blood pressure. These variables are known to be related to cardiovascular complications and/or fatty liver disease. Therefore, tofogliflozin may be beneficial for patients who already have these complications of diabetes.

Limitations of our trial include the open-label design, the small number of patients and short duration. Use of BIA for evaluation of body composition may also be a limitation. This is because, compared with measurement by dual x-ray absorptiometry (DXA), BIA indirectly calculates values using an equation developed on the basis of DXA data. In addition, although the validity of BIA has been extensively studied, there are factors influencing BIA evaluation.[20] Endpoints other than the primary one were exploratory because their α errors could not be controlled. We only studied patients with moderately high body fat percentages. Changes in body fat percentage and fat-free mass in patients with lower or higher values for these variables merit study.

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CONFLICT OF INTEREST

T.K. has received lecture fees from Sanofi and Ono Pharmaceutical. H.S. has received grants from Nippon Boehringer Ingelheim, AstraZeneca, Sanofi, Sanwa Kagaku, MSD, Japan Tobacco Inc., Taisho Pharmaceutical, Novo Nordisk Pharma, YL Biologics and Mitsubishi Tanabe Pharma. M. Ai has received lecture fees from Sanofi and MSD, and has received grants from DENKA SEIKEN Co., Ltd. and Skylight Biotech Inc. M.F. has received a grant from Life Scan Japan. H.K. has received lecture fees from MSD and Takeda Pharmaceutical. M. Anai has received a donation from CliniPro Co. H.I. has served on the advisory board of Astellas Pharma, has received lecture fees from Astellas Pharma, MSD, Mitsubishi Tanabe Pharma, Nippon Boehringer Ingelheim and Novartis Pharma, and has received grants from Ono Pharmaceutical, Nippon Boehringer Ingelheim, Sanofi, Mitsubishi Tanabe Pharma, Eli Lilly, Daiichi-Sankyo, Novo Nordisk Pharma and MSD. H.O., T.I., M.I. and M.Y. have nothing to declare.

AUTHOR CONTRIBUTIONS

H.I., M. Anai and H.S.: conception and design of the trial, enrolment of patients and acquisition of data; M.F., T.K., T.I., M.Y., M.I., H.O., H.K. and M. Ai: enrolment of patients and acquisition of data. All authors read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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