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ORIGINAL RESEARCH

Up-Titration Strategy After DPP-4 Inhibitor-Based Oral Therapy for Type 2 Diabetes: A Randomized Controlled Trial Shifting to a Single-Dose GLP-1 Enhancer Versus Adding a Variable Basal Insulin Algorithm

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ABSTRACT

Introduction: It is unclear whether adding basal insulin or enhancing incretin signaling with a glucagon-like peptide-1 receptor agonist (GLP-1RA) is more effective as an up-titration strategy after dipeptidyl peptidase-4 inhibitor (DPP-4i)-based oral antidiabetic drug (OAD) therapy. GLP-1RAs can be injected without dose adjustment, unlike basal insulin. Our objective was to examine the efficacy of changing patients inadequately controlled with oral DPP-4i-based OAD therapy to injectable GLP-1RA and discontinuing the DPP4i versus adding basal insulin glargine (IGlar) with the continuation of the oral DPP4i.

Methods: Sixty patients with type 2 diabetes (T2DM) and glycated hemoglobin (HbA1c) between 7.0% and 10.0% on DPP-4i-based OAD therapy were randomized to either adding IGlar and remaining on the DPP-4i or liraglutide and discontinuing the DPP-4i for 24 weeks. Patients in the IGlar group started with 0.1 unit/kg and were titrated according to the algorithm. In the liraglutide group, the DPP-4i was replaced with liraglutide 0.9 mg/day, the maximum dose in Japan. We evaluated HbA1c, glycated albumin (GA), and anthropometrics.

Results: HbA1c was significantly lower at week 24 ($-1.0 \pm 0.9\%$ in the IGlar group and

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− 0.6 ± 0.8% in the liraglutide group), but the difference between groups was not significant. Changes in GA were similar (− 2.9 ± 3.2% vs. − 2.6 ± 3.2%) in both groups. Body weight (BW) was significantly lower only in the liraglutide group (+ 0.5 ± 2.6 kg vs. − 2.2 ± 2.0 kg). The rate of minor hypoglycemic episodes was similar for both groups. **Conclusion**: For poorly controlled T2DM on DPP-4i-based OAD therapy, switching to single-dose liraglutide to enhance incretin signaling is as effective as dose-titrated basal IGlar, but significant BW reduction was only seen in the liraglutide group. These results suggest that enhancing incretin signaling with a single-dose injectable GLP-1 RA might be an alternative to dose-titrated basal insulin therapy in patients with T2DM poorly controlled with DPP-4i-based OAD therapy. These findings should be confirmed in a longer and larger trial. **Trial Registration**: Trial Registry (UMIN-CTR) as UMIN000012224.

Keywords: Dipeptidyl peptidase-4 inhibitor; Glargine; Liraglutide

INTRODUCTION

To reduce the risk of long-term diabetic complications, guidelines in Europe, the USA, and Japan have recommended early partitioning of injectable therapy as part of stepwise intensification of treatment to reduce glycated hemoglobin (HbA1c) below the target of 7.0% (53 mmol/mol) [1–4]. As part of an up-titration algorithm, insulin is the next choice of medication to achieve a HbA1c target below 7.0% after oral antidiabetic drugs (OADs). However, use of insulin is not widespread because of fears of hypoglycemia and challenges in dose titration.

Incretin is a hormone that controls glucose metabolism via an intestinal signal that senses various nutritional stimuli [5]. Glucagon-like peptide-1 (GLP-1) analogues are alternatives to insulin as additions to OAD therapy. Gliptins, a relatively new class of OADs, act by inhibiting dipeptidyl peptidase-4 (DPP-4), which inactivates incretins, namely glucose-dependent

insulinotropic polypeptide (GIP) and GLP-1 [5]. Incretin-based therapies are attracting attention in terms of treatment efficacy, cost-effectiveness, and improved cardiovascular outcomes for patients with type 2 diabetes mellitus (T2DM) [6–8]. Two types of incretin-based therapy are now available to treat T2DM: injectable GLP-1 receptor agonists (GLP-1RAs, incretin mimetics) and oral DPP-4 inhibitors [9]. DPP-4 inhibitors are the most commonly prescribed OADs in Japan, taken by more than 70% of patients with T2DM [10]. Incretin-based therapy is thought to be more effective for T2DM in Asian populations than non-Asian counterparts [11–13]. However, there are many patients who are inadequately controlled with DPP-4 inhibitors.

Basal insulin or GLP-1RA injections have generally been accepted as second- or third-line therapy in American Diabetes Association/European Association for the Study of Diabetes consensus statements [2]. Earlier introduction of injection therapy is desired in patients with diabetes poorly controlled with OADs. Two studies showed that switching from sitagliptin to liraglutide in T2DM has a similar effect on the HbA1c, although the active comparator was a DPP-4 inhibitor [14, 15]. Unlike insulin, GLP-1RAs can be injected without dose adjustment. However, when using GLP-1RAs, we must pay attention to tachyphylaxis [16]. It is also unclear why changes in mean HbA1c and fasting plasma glucose (FPG) levels occur after the third month of intervention and the effect may occur later.

It remains unclear which injections are better as an additional treatment option for T2DM when OADs, including DPP-4 inhibitors, do not provide adequate control in terms of achieving target HbA1c: basal-supported oral therapy (BOT) with insulin or switching to a GLP-1RA to strengthen incretin-based therapy. It is also unclear whether GLP-1 incretin enhancement remains an option after oral incretin or DPP-4 inhibitor therapy. Therefore, we performed this 24-week randomized controlled study to find out whether adding basal insulin glargine U100 (IGlar) or switching to liraglutide is more likely to be an option for achieving HbA1c below 7.0% and better in terms of patient safety.

METHODS

Study Design

This 24-week, multicenter, open-label, randomized, parallel-group trial took place at six sites (university hospitals and diabetes clinics). Participants were enrolled between June 2013 and December 2015. Inclusion criteria included T2DM with inadequate glycemic control despite diet and exercise therapy and OADs consisting of a DPP-4 inhibitor with metformin, sulfonylureas (SUs), glinides, alpha-glucosidase inhibitors, or thiazolidinediones.

Sixty T2DM patients treated with OADs, including a DPP-4 inhibitor in addition to lifestyle modification for 12 or more weeks, were randomized to either IGlar or liraglutide once daily in a 1:1 ratio for a 24-week intervention period (Fig. 1). The randomization scheme, incorporating a random number generator, was produced by an independent researcher who was not directly involved in data collection or delivery of the study drugs. Randomization was performed using the minimization method with HbA1c (%) and age. Four or more weeks before the start of this trial, after written informed consent was obtained, all types of DPP-4 inhibitors were replaced with 50 mg of sitagliptin daily and SUs were changed to 1 mg of glimepiride, the highest prescribed dose in Japan for each class, to minimize the effect of individual drugs. To evaluate the impact of the two investigational treatments, adding basal insulin (IGlar) with the oral incretin sitagliptin versus the injectable incretin liraglutide, we aimed to structure OAD therapy to the same extent prior to the beginning of the intervention. Most of the subjects in this study were treated with glimepiride 1 mg, but one subject in each group was prescribed 2 mg. Neither subject had been taking other SUs such as glibenclamide or gliclazide before the study period. The change in HbA1c from more than 4 weeks before the intervention to the end of the run-in period was not statistically significantly different (IGlar group, $8.19 \pm 0.84\%$ to $8.27 \pm 1.01\%$; liraglutide group, $8.06 \pm 0.46\%$ to $8.16 \pm 0.46\%$; $P = 0.22$). The change in glycated albumin over the same period was similar between the two groups (IGlar group, $21.0 \pm 2.68\%$ to $20.8 \pm 3.58\%$; liraglutide group, $22.4 \pm 4.14\%$ to $21.0 \pm 3.73\%$; $P = 0.40$). Patients visited the hospital or clinic once every 2 weeks up to week 8 for dose adjustments; thereafter, visits were every 4 weeks. The IGlar group was started at 0.1 unit/kg and titrated up according to an algorithm to a target FPG of less than 110 mg/dL (6.1 mmol/L) without discontinuing sitagliptin (Table 1). In the liraglutide group, sitagliptin was replaced by liraglutide at a starting dose of 0.3 mg, which was increased by 0.3 mg at least once weekly so the final dose was 0.9 mg, the maximum dose in Japan, by week 12, which was continued until the end of the trial. Blood samples were collected after an overnight fast at visits every 4 weeks. As a general rule, we did not change OADs during the trial period unless hypoglycemia occurred.

Participants

We included Japanese men and women with T2DM for at least 6 months, who were at least 20 years of age, currently treated with OADs for at least 12 weeks, and had HbA1c levels ranging from 7.0% to less than 10%. Subjects were
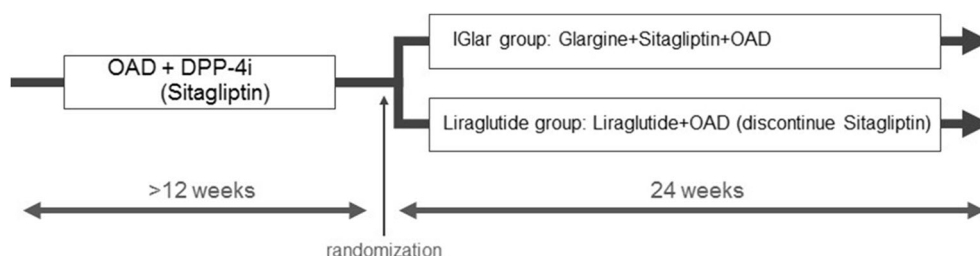

Fig. 1 Study design. DPP-4i dipeptidyl peptidase-4 inhibitor, OAD oral antidiabetic drug, IGlar insulin glargine

Table 1 IGlar dose adjustment algorithm

FPG (mg/dL)	IGlar dose
≥ 200	+ 4 units
140–199	+ 2 units
110–139	+ 1 unit
81–109	No change
< 80	− 1 or 2 units
Hypoglycemic symptom	

IGlar insulin glargine, *FPG* fasting plasma glucose

excluded if they had been treated with insulin or GLP-1RA injection therapy, or had impaired renal or hepatic function, pancreatic disease, malignancy (either known or previous malignancy and strongly suggestive of recurrence), significant cardiovascular disease (heart failure or coronary artery disease) within 3 months, or unstable proliferative retinopathy.

All study protocols and procedures were in accordance with the ethical standards of the Ethics Committee of the Toho University Omori Medical Center Hospital and the 1964 Helsinki Declaration and its amendments. The study objectives and intended measures were explained to all the participants individually. Informed consent was obtained from all study participants.

Endpoints and Assessments

The primary endpoints were the change in HbA1c from baseline to week 24 and the proportion of patients achieving HbA1c below 7% at week 24. Secondary efficacy endpoints included change in HbA1c regarding taking SUs or not, and change in body weight (BW). Secondary safety endpoints assessed over 24 weeks included the number of hypoglycemic episodes. The sample size calculation assumed a mean difference in the change in HbA1c between the two groups of 0.18% and a standard deviation (SD) of 0.22%, based on the results of two prior studies of basal insulin compared to GLP-1 analogue therapy [17, 18]. At a significance level of 5% and power of 80%, 18 patients were

required (24 per group). Therefore, we planned to enroll 30 patients per group to account for potential loss to follow-up.

Statistical Analysis

The results are expressed as means ± SD. Differences between groups were first estimated using one-way analysis of variance (ANOVA), the chi-squared test, or the *t* test for comparison. When a significant effect was found with ANOVA, the results were further compared using the Bonferroni multiple range test. Cochran–Mantel–Haenszel (CMH) modeling was used to analyze the proportion of patients who achieved the HbA1c target at week 24, with or without SUs. Differences were considered to be significant with a two-sided $P < 0.05$.

This trial was registered with the University Hospital Medical Information Network-Clinical Trials Registry (UMIN-CTR) as UMIN000012224.

RESULTS

In the IGlar group, three subjects withdrew consent. The trial was stopped in one subject at the discretion of the physician because of high glucose levels. In the liraglutide group, one subject withdrew consent. These five subjects were excluded from the analysis (Fig. 2).

Baseline characteristics of the study patients are summarized in Table 2. The mean dose of IGlar was 6.5 ± 2.8 units at the start of the trial, which was titrated to 14.4 ± 9.1 units at the end of the trial (range, 6–40 units/day). The dose of liraglutide was increased to 0.9 mg in all subjects by week 8, but two subjects had dose reductions to 0.6 mg because of adverse effects (gastrointestinal symptoms). Although we did not plan to introduce self-monitoring of blood glucose for subjects, we approved it for the five subjects in the IGlar group and two subjects in the liraglutide group who wished to do so ($P = 0.17$).

The mean change in HbA1c from baseline to week 24 was significant in both groups (− 1.0 ± 0.9% in the IGlar group and − 0.6 ± 0.8% in the liraglutide group) but there
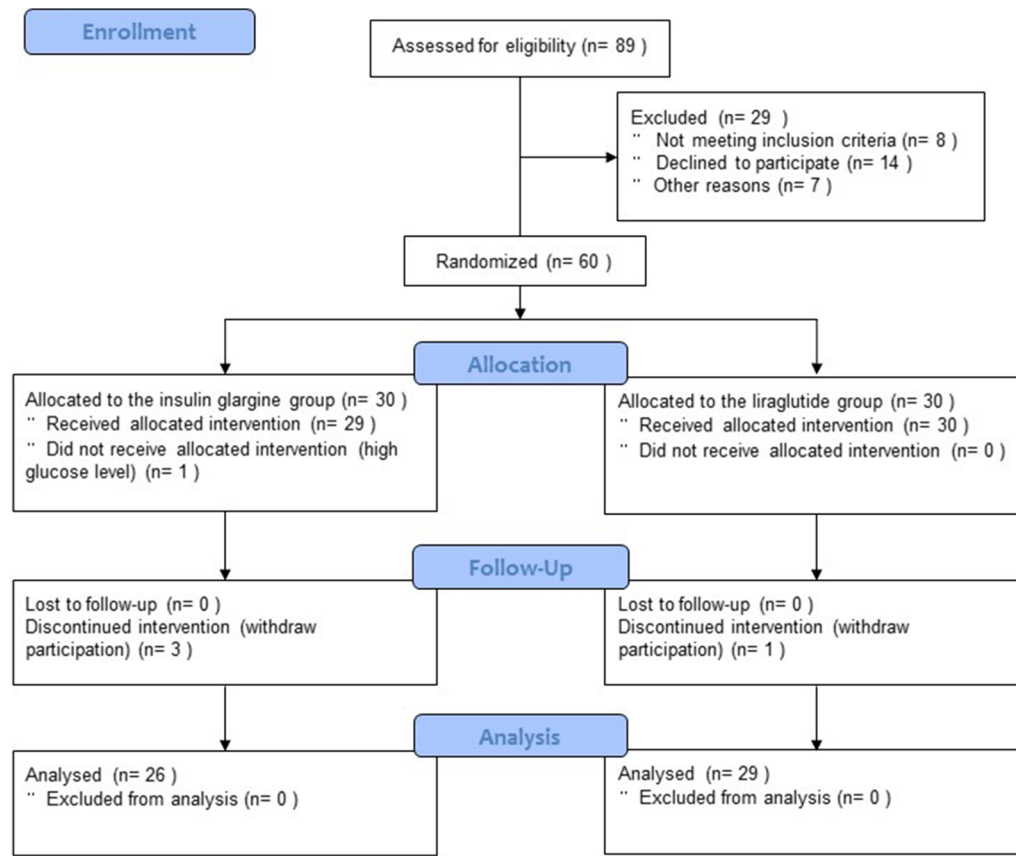
Fig. 2 Study flow diagram

was no statistically significant difference between the groups ($P = 0.16$; Fig. 3a). Results were similar for glycated albumin (GA) (mean change $- 2.9 \pm 3.2\%$ in the IGlar group and $- 2.6 \pm 3.2\%$ in the liraglutide group; $P = 0.53$; Fig. 3b). The proportion of patients who achieved HbA1c below 7% at week 24 was not statistically significant different (42.3% in the IGlar group and 24.1% in the liraglutide group; chi-squared $P = 0.15$, CMH $P = 0.25$; Supplementary Fig. S1). We examined changes in HbA1c with or without SUs separately, but there was no statistically significant difference (Supplementary Fig. S2).

Mean BW was significantly increased from baseline in the IGlar group ($+ 0.5 \pm 2.6$ kg), whereas in the liraglutide group it decreased significantly ($- 2.2 \pm 2.0$ kg) (Table 3), but the difference between groups was not significant ($p = 0.37$).

A few minor hypoglycemic episodes occurred in both groups (four episodes in the IGlar group and three in the liraglutide group; $P = 0.58$). The minimum FPG level was 77 mg/dL, which occurred in the IGlar group. Lipid parameters, as well as human immunoreactive insulin and proinsulin levels, were similar to baseline levels and between groups (Table 3). Blood pressure in the two groups was similar during the study period.

DISCUSSION

Injectable After Oral Incretin Therapy

We wish to find room to enhance incretin signaling to improve glucose control in patients with primary OAD failure, including DPP-4 inhibitors, compared to BOT. In this study, we showed the efficacy of an up-titration strategy

Table 2 Characteristics of baseline

	IGlar group	Liraglutide group	P value
Number (gender)	26 (M16/F10)	29 (M18/F11)	0.968
Age (years)	60.6 ± 13.2	63.9 ± 10.4	0.303
Body weight (kg)	71.5 ± 18.7	69.8 ± 14.3	0.697
BMI (kg/m^2)	26.4 ± 5.1	26.6 ± 4.0	0.870
Duration of diabetes (years)	13.0 ± 7.5	11.9 ± 6.1	0.537
eGFR (mL/min/1.73 m^2)	79.9 ± 15.4	73.2 ± 14.9	0.143
HbA1c (%)	8.3 ± 0.8	8.2 ± 0.5	0.623
SUs (glimepiride)	17 (65.4%)	22 (75.9%)	0.374
Glinides	0 (0.0%)	2 (0.7%)	0.173
α-GIs	3 (11.5%)	3 (10.3%)	0.887
TZD	6 (23.1%)	2 (0.7%)	0.089
BGs	17 (65.4%)	14 (48.3%)	0.201
OAD ≥ 2 types combined	24 (92.3%)	28 (96.6%)	0.489

Data are expressed as the mean ± standard deviation. P value indicates comparison between groups

BMI body mass index, *eGFR* estimated glomerular filtration rate, *HbA1c* glycated hemoglobin, *SUs* sulfonylureas, *α-GIs* alpha-glucosidase inhibitors, *TZD* thiazolidinedione, *OAD* oral antidiabetic drug

for T2DM that was inadequately controlled with DPP-4 inhibitors and other OADs. Adding a single-dose GLP-1 incretin enhancement had a therapeutic effect that was similar to the effect of adding dose-titrated basal insulin. Parallel analysis of a series of predefined parameters related to glucose control showed that adding a single-dose GLP-1 analogue (i.e., changing an oral incretin to an injectable incretin) and adding dose-titrated basal insulin treatment had similar effects. However, BW reduction was only observed with single-dose GLP-1 analogue therapy. The clinical safety and efficacy profile of GLP-1 analogues compared to insulin has been assessed in several meta-analyses [19, 20]. However, at this point, GLP-1 analogue therapy
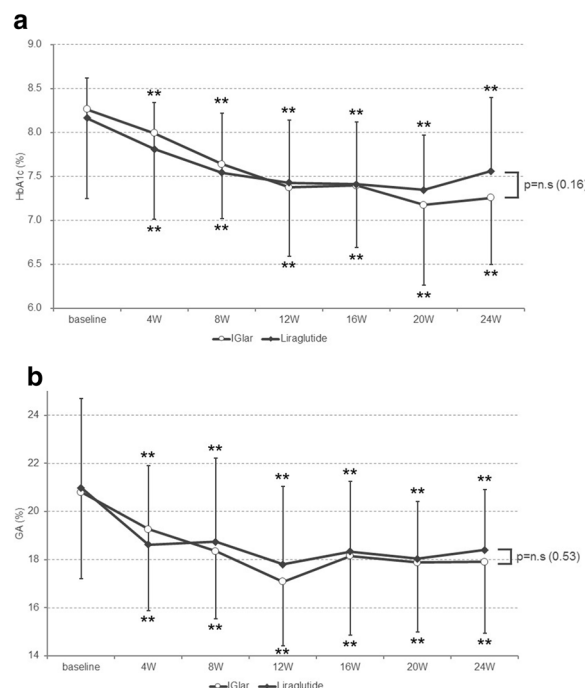
Fig. 3 Mean change in **a** HbA1c and **b** glycated albumin levels. Open circles indicate mean levels in the insulin glargine (IGlar) group and closed diamonds indicate mean levels in the liraglutide group. Error bars indicate standard deviation. Asterisks denote significance (**$P < 0.01$ vs. baseline)

after insufficient OAD therapy might be considered as an alternative to basal insulin treatment used as an adjunct to OADs. Therefore, there is an increasing desire to understand the possibilities and limitations of GLP-1 analogues and basal insulins.

Efficacy Analysis

Adding titrated basal insulin to oral therapy is typically indicated when HbA1c is 1.5–2.0% above target HbA1c in patients with T2DM [21]. Our trial investigated the effectiveness of a simple fixed-dose incretin enhancement to multiple OAD therapy, which was designed to support the initiation of injection therapy in patients with T2DM in the primary care setting. Furthermore, we aimed to set simple clinical protocols compared to the dose-titration algorithms used when initiating basal insulin. Regarding reducing hyperglycemia, mean

Table 3 Results and comparison between groups or with baseline

	IGlar	Liraglutide	Comparison between groups P value	Comparison with baseline	
				IGlar P value	Liraglutide P value
Body weight (kg)					
Baseline	71.5 ± 18.7	69.8 ± 14.3	0.697		
24-week	72.0 ± 20.3	67.6 ± 14.0	0.369	0.047	< 0.001
Waist circumference (cm)					
Baseline	90.4 ± 10.3	93.0 ± 11.2	0.470		
24-week	95.4 ± 14.1	91.4 ± 11.8	0.365	0.053	0.689
FPG (mg/dL)					
Baseline	177.8 ± 65.6	173.8 ± 39.0	0.785		
24-week	145.2 ± 42.3	152.9 ± 30.1	0.449	0.018	0.024
LDL-C (mg/dL)					
Baseline	94.0 ± 22.8	109.0 ± 35.8	0.111		
24-week	87.0 ± 33.4	101.0 ± 35.3	0.192	0.436	0.465
HDL-C (mg/dL)					
Baseline	55.5 ± 16.1	55.8 ± 14.1	0.941		
24-week	53.8 ± 15.9	56.1 ± 12.9	0.600	0.731	0.947
TG (mg/dL)					
Baseline	144.6 ± 85.1	159.3 ± 57.8	0.658		
24-week	150.0 ± 98.6	161.8 ± 62.9	0.642	0.848	0.892
Human IRI (μIU/mL)					
Baseline	24.8 ± 29.6	18.2 ± 15.4	0.333		
24-week	29.6 ± 56.7	15.8 ± 11.3	0.251	0.743	0.533
Human pro-insulin (pmol/L)					
Baseline	56.0 ± 76.1	32.5 ± 17.5	0.161		
24-week	61.4 ± 101.2	25.3 ± 15.5	0.168	0.869	0.190

FPG fasting plasma glucose, *LDL-C* low-density-lipoprotein cholesterol, *HDL-C* high-density-lipoprotein cholesterol, *TG* triglyceride, *IRI* immunoreactive insulin

changes in HbA1c from baseline to week 24 were not significantly different between the two groups. The rates of achieving HbA1c below 7.0% after 24 weeks of treatment, as recommended in international guidelines, were 24% in the simple fixed-dose GLP-1 analogue group and 42% in the titrated basal insulin group ($P = 0.15$), suggesting that intensifying incretin signaling and oversupplying basal insulin were not sufficient to achieve optimized glycemic control. IGlar was used as an adjunct to DPP4 inhibitor-based OAD therapy. In this study,

physicians specializing in diabetes treatment tried to titrate the dose of IGlar on the basis of an algorithm to achieve a target FPG level of less than 110 mg/dL (6.1 mmol/L), in contrast to patients adjusting the basal insulin IGlar dose frequently. Study visits occurred at intervals of 2–6 weeks, which might not be effective at lowering fasting plasma glucose. The reason for poor achievement, including a sedentary lifestyle, might be related to patient factors. Inclusion criteria for this trial included resistance to multiple drugs for controlling blood glucose. In diabetes management, inability to improve glycemia with the addition of a GLP-1 analogue and basal insulin suggests that multiple daily injections are imperative in some patients inadequately controlled with OADs.

Limitations

The present study has some limitations. First, this was an open-label trial, as a result of different titration algorithms for basal insulin and the GLP-1 analogue, which would have led to more investigator or participant bias. Second, at the end of the 24-week trial, the proportion of subjects who achieved HbA1c below 7.0% was relatively low, 24–42%, suggesting that most subjects might eventually need multiple injections daily. However, this rate was similar to the rate in a previous trial comparing the effect of IGlar to liraglutide in patients with OAD failure, who were not taking DPP-4 inhibitors [22]. The small sample size probably explains why reduced BW was seen in the IGlar group and there were very limited safety and efficacy concerns. Finally, we could not figure out the mechanism of action that explains the differences between adding basal insulin and GLP-1 analogue injection in patients with OAD failure. Hypoglycemia was seen in both groups to the same extent. The structure and dynamics of hypoglycemia should be monitored using a continuous glucose monitoring system in future studies, which we did not use. To address these limitations, a larger sample size and continuous glucose monitoring should be used to investigate the rate of hypoglycemia.

CONCLUSIONS

For patients with T2DM inadequately treated with OADs including DPP-4 inhibitors, either adding IGlar or switching to liraglutide is safe and effective, but significant BW reduction was only observed in the liraglutide group. Our results suggest that liraglutide can be a good treatment option for such patients because, unlike IGlar, it is effective without dose adjustment. Given the short study period and small sample size, future studies with more participants are needed to confirm the results of this study.

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