



Original Article

Efficacy of Combination of Insulin Glargine with either Metformin or Sulfonylurea in Patients with Poorly Controlled Type 2 Diabetes

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SUMMARY

Background: Although adding insulin glargine to oral antidiabetic drugs (OADs) has demonstrated efficacy in patients with type 2 diabetes, evidence supporting specific regimens is lacking. The aim of this study was to compare the efficacy of combination therapy of insulin glargine with either sulfonylurea (SU) or metformin (Met) in patients with poorly controlled type 2 diabetes receiving ≥ 2 OADs.

Methods: This was a 48-week prospective, open-label, randomized, parallel trial. Patients with type 2 diabetes poorly controlled with ≥ 2 OADs were randomized to the insulin glargine with Met (Met-group) or insulin glargine with SU (SU-group).

Results: Mean glycosylated hemoglobin (A1C) reduction were significant in the Met-group and SU-group ($-1.42 \pm 0.28\%$ and $-1.00 \pm 0.28\%$, respectively), but no statistically significant difference between groups ($-0.40 \pm 0.3\%$, $p = 0.234$). There was no difference in the proportion of patients achieving A1C of $< 7\%$ (12.8% and 6.8%, respectively). Mean FPG reduced significantly in both groups (-120.3 ± 8.8 mg/dL and -90.2 ± 11.1 mg/dL, respectively), with greater reductions in the Met-group (-34.8 ± 10.0 mg/dL, $p < 0.001$). More proportions of patients in the Met-group achieved the FPG target of < 130 mg/dL (80.9% and 40.9%, respectively, $p < 0.001$). The percentages of patients experiencing episodes of symptomatic hypoglycemia (Met-group: 23.4%, SU-group: 19.6%) and the percentages of nocturnal hypoglycemia (Met-group: 8.5%, SU-group: 6.5%) were similar among the two groups.

Conclusion: In patients with type 2 diabetes poorly controlled on ≥ 2 OADs, glycemic control was comparable among the two regimens.

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1. Introduction

Effective glycemic control plays an important role in preventing chronic complications of diabetes mellitus.^{1,2} Although lifestyle change and oral antidiabetic drugs (OADs) can improve glycemic control early in the course of type 2 diabetes.^{3,4} However, type 2 diabetes is a progressive illness in which most patients experience a progressive deterioration in glycemic control, eventually requiring the addition of exogenous insulin treatment.⁵

Combination therapy with basal insulin and OADs can be managed at outpatient clinics and simple subject-administered titration algorithm can be used after education.^{6–13} Insulin glargine exhibits a 24-hour action profile with no pronounced peak and its advantages of combination with sulfonylurea (SU) alone, metformin alone, or SU with metformin in type 2 diabetes poorly controlled on OADs have been demonstrated.^{6–14} Despite the increasingly complex management of patients with diabetes, basal insulin remains one of the most effective medications to reduce hyperglycemia and is a recommended option that can be combined with almost all other type 2 diabetes medications.^{15–17}

Combination therapy with basal insulin and OADs can safely improve glycemic control; however, there is uncertainty regarding which regimen to choose when using basal insulin plus OADs in order to achieve better glycemic control in type 2 diabetes patients previously poorly controlled with multiple OADs. The aim of this study was to compare the efficacy of combination therapy of insulin glargine with either sulfonylurea (SU) or metformin in patients with poorly controlled type 2 diabetes receiving ≥ 2 OADs.

2. Materials and methods

2.1. Patient selection and study design

This investigator-initiated prospective, open-label, randomized, parallel, 48-week comparative study was performed at the Mackay Memorial Hospital, Taipei, Taiwan. It was conducted in accordance with the Declaration of Helsinki and approved by the ethics board of Mackay Memorial Hospital. Informed consent was obtained from all the subjects included in the study.

Enrolled subjects were type 2 diabetes patients who were treated with maximally tolerated dose of SU (i.e., glibenclamide 20 mg/d, gliclazide 320 mg/d, and glimepiride 8 mg/d) and metformin ($> 1,500$ mg/d) with or without other class of OADs for > 12 weeks.

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Inclusion criteria were age 20 years or older, glycosylated hemoglobin (A1C) $\geq 7.5\%$ and fasting plasma glucose (FPG) ≥ 130 mg/dL at the time of screening. Exclusion criteria were previous use of insulin, hypersensitivity to insulin, New York Heart Association class III or IV heart failure, myocardial infarction or stroke in the past 6 months, active liver disease, current glucocorticoid use, and pregnancy or breastfeeding. Patients were allowed to use anti-hypertensive or lipid-lowering drugs if they had been taking a stable dose for > 12 weeks prior to the study and no changes were made in their therapy during the study. Withdrawal criteria included pregnancy, A1C $> 12.0\%$ after the first 12 weeks of treatment, weight gain or edema unacceptable to the patient, or serious adverse effects, including heart failure and hepatic failure.

Eligible patients were randomized in a 1:1 ratio to either the SU-group (insulin glargine + SU) or the Met-group (insulin glargine + metformin). The randomization was performed using an interactive voice-response system that used a permuted-block size of 6. In addition, patients were stratified by A1C (7.5% to 9.0% and $> 9.0\%$). Throughout the entire study, patients maintained the same dose of the single class of OAD they were on prior to the study. All subjects received a single daily injection of insulin glargine at bedtime with a starting dose of 0.4 IU/kg/day. The goal was to achieve a FPG of 70–130 mg/dL. Patients were taught to increase their daily insulin doses by 2 IU if the FPG was > 130 mg/dL, and by 4 IU if the FPG was > 180 mg/dL on 3 consecutive days without any intervening hypoglycemic episodes; or decrease the daily insulin dose by 4 IU if the FPG was < 70 mg/dL. Doses of OAD remained unchanged throughout the study. Subjects visited the research site at baseline and at 4, 12, 24, 36, and 48 weeks and were also contacted by telephone at 1, 2, and 3 weeks to discuss adjustments in insulin dose. Throughout the course of the study, patients were instructed to continue the same lifestyle, including diet and exercise, they had maintained prior to entering the study.

2.2. Objectives

The primary objectives were to compare the glycemic control (A1C) between different treatment regimens. Secondary objectives included assessment of changes in FPG, proportion of patients achieving A1C $< 7\%$, change in weight, and mean insulin dose. Safety was assessed by the proportions of patients who developed hypoglycemic events. Symptomatic hypoglycemia was defined as an event with clinical symptoms consistent with hypoglycemia and nocturnal hypoglycemia as symptomatic hypoglycemia occurring while the patient was asleep, after the evening insulin injection and before getting up in the morning. Severe hypoglycemia was defined as an event with symptoms consistent with hypoglycemia in which the patient required the assistance of another person and was associated with either a plasma glucose level less than 50 mg/dL or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration.

2.3. Outcome measurement

A1C, FPG and weight were measured at baseline, weeks 12, 24, 36 and 48. Plasma C-peptide, ALT, total cholesterol, triglyceride, LDL cholesterol, HDL cholesterol were measured at baseline.

2.4. Statistical analysis

An intent-to-treat (ITT) analysis with last observation carried forward was used to assess efficacy. The ITT population included all

patients who had received at least one dose of study medication and had A1C recorded at baseline and at least once after baseline. Treatment groups were compared at baseline using the Student t test for continuous variables and the Chi-square test for categorical variables. The change from baseline in continuous parameters were determined using an analysis of co-variance (ANCOVA) model with the factor ‘treatment’ and baseline value as covariate. The chi-square test or Fisher’s exact test were used for dichotomous parameters. All patients who had taken at least one dose of study medication were included in the safety analysis. Results were presented as mean (\pm SD) or numbers or percentages for dichotomous parameters. All analyses were done using SAS version 9.4.

3. Results

Figure 1 summarizes patients flow through the study. A total of 115 patients were screened, 96 were enrolled (Met-group, $n = 48$; SU-group, $n = 47$), and a similar number of patients in each treatment group completed the 48-week treatment. The reasons for premature withdrawal included being lost to follow-up (1 in Met-group and 3 in SU-group), protocol violation (2 in Met-group and 3 in SU-group). Baseline characteristics and demographics were similar among the two treatment groups (Table 1).

Both Met-group and SU-group significantly decreased A1C from baseline to endpoint ($-1.42 \pm 0.28\%$ and $-1.00 \pm 0.28\%$, respectively), but no statistically significant difference between the treatment groups was observed ($-0.40 \pm 0.3\%$, $p = 0.234$) (Table 2 and Figure 2). Both groups showed significant reductions in mean FPG over 48 weeks (-120.3 ± 8.8 mg/dL in the Met-group and -90.2 ± 11.1 mg/dL in the SU-group), with significantly greater reductions in the Met-group compared with the SU-group (-34.8 ± 10.0 mg/dL, $p < 0.001$). Figure 2 shows changes during the course of the study for A1C and FPG levels. A greater proportion of patients in the Met-group achieved the FPG target of < 130 mg/dL compared to the SU-group (80.9% vs. 40.9%, respectively, $p < 0.001$). The percentages of patient achieving an A1C $< 7\%$ was similar in both groups (12.8% in the Met-group and 6.8% in the SU-group). A total of 27 elderly patients (≥ 65 years) in this study. Post hoc analysis showed no difference in A1C changes between elderly and non-elderly patients in the Met-group and SU-group ($-1.73 \pm 0.52\%$ vs. $-1.28 \pm 0.34\%$ and $-1.05 \pm 0.53\%$ vs. $-0.98 \pm 0.34\%$, respectively).

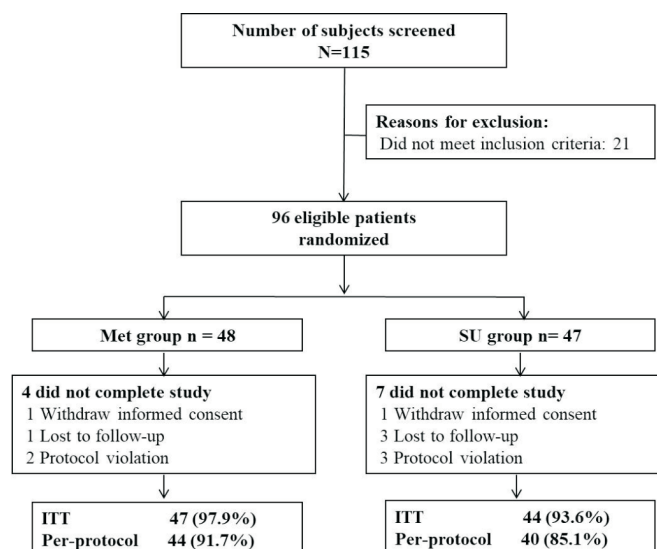


Figure 1. Patient flow through the study. Met, metformin; SU, sulfonylurea; ITT, intent-to-treat.

Table 1
Baseline demographic and clinical characteristics.

Characteristic	Met group (n = 47)	SU group (n = 46)
Female, n	30 (63.8%)	31 (67.4%)
Age, years	59.3 ± 9.7	55.0 ± 14.1
Duration of diabetes, years	11.2 ± 5.8	9.9 ± 6.0
Weight, kg	65.0 ± 13.0	63.9 ± 15.3
Body-mass index, kg/m ²	25.7 ± 4.0	25.2 ± 4.3
A1C, %	10.3 ± 1.6	10.3 ± 1.5
FPG, mg/dL	234.5 ± 49.8	239.5 ± 51.4
C-peptide, ng/mL	2.99 ± 1.70	2.86 ± 1.79
eGFR, mL/min/1.73 m ²	74.6 ± 17.6	70.6 ± 14.2
ALT, IU/L	32.3 ± 40.3	36.2 ± 37.3
Total cholesterol, mg/dL	211.7 ± 41.2	212.5 ± 39.4
Triglyceride, mg/dL	200.7 ± 134.7	201.8 ± 126.8
LDL cholesterol, mg/dL	132.2 ± 36.5	131.5 ± 37.9
HDL cholesterol, mg/dL	50.3 ± 22.2	47.3 ± 21.2
Metformin, mg/day	2245 ± 616	2114 ± 493
Thiazolidinedione, n	10 (21.3%)	11 (25.0%)
Sulfonylurea, n	47 (100%)	44 (100%)
Glibenclamide, n	6 (12.8%)	7 (15.9%)
Gliclazide, n	8 (17.0%)	10 (22.7%)
Glimepiride, n	33 (70.2%)	27 (61.4%)
Insulin dose, U/day	25.4 ± 4.9	24.5 ± 5.9
Insulin dose, U/kg/day	0.39 ± 0.03	0.39 ± 0.03

Data are n (%) or mean ± SD.

A1C, glycosylated hemoglobin; FPG, fasting plasma glucose; ALT, alanine-aminotransferase; eGFR, estimated Glomerular filtration rate (MDRD).

* p < 0.05.

Table 2

Least squares mean change from baseline in primary and secondary outcomes for the intent-to-treat population.

Characteristics	Mean change from baseline				Between group difference	
	Met group (N = 47)	p	SU group (N = 44)	p	p	
A1C change from baseline (%)	-1.42 ± 0.28	< 0.001	-1.00 ± 0.28	0.001	-0.40 ± 0.33	0.237
FPG change from baseline (mg/dL)	-120.3 ± 8.8	< 0.001	-90.2 ± 11.1	< 0.001	-34.8 ± 10.0	< 0.001
BW change from baseline (kg)	3.7 ± 0.42	< 0.001	3.3 ± 0.43	< 0.001	0.43 ± 0.60	0.478
Insulin dose change from baseline (U/day)	15.4 ± 2.1	< 0.001	18.3 ± 2.6	< 0.001	-3.6 ± 3.2	0.274

A1C, glycosylated hemoglobin; FPG, fasting plasma glucose; BW, body weight.

At the end of the study, both Met-group and SU-group significantly increased insulin dose from baseline (15.4 ± 2.1 U/day and 18.3 ± 2.6 U/day, respectively), but no statistically significant difference between the treatment groups was observed (-3.6 ± 3.2 U/day, p = 0.274). The mean daily insulin doses were comparable in the two groups: 0.62 ± 0.22 U/kg in the Met-group and 0.67 ± 0.24 U/kg in the SU-group. Although there was an increase in average weight in both Met-group and SU-group after 48 weeks of treatment (3.7 ± 0.4 kg and 3.3 ± 0.4 kg, respectively), no statistically significant difference between the two groups was observed (-0.4 ± 0.6 kg, p = 0.478)

The percentages of patients experiencing episodes of symptomatic hypoglycemia (Met-group: 23.4%, SU-group: 19.6%) and the percentages of patients experiencing nocturnal hypoglycemia (Met-group: 8.5%, SU-group: 6.5%) were similar among the two groups. There was only one episode of major hypoglycemia during the entire study period, which occurred in the Met-group.

4. Discussion

Basal insulin was recommended as the first option of insulin for patients whose disease is not controlled by OADs.^{15,16,18} Some consensus recommend that when insulin injection is started, insulin secretagogues should be discontinued or tapered and then discontinued.^{15,18} This study showed there were no significant differences in the average reduction of A1C among Met-group and SU-group. Although the mean A1C values and the proportions of

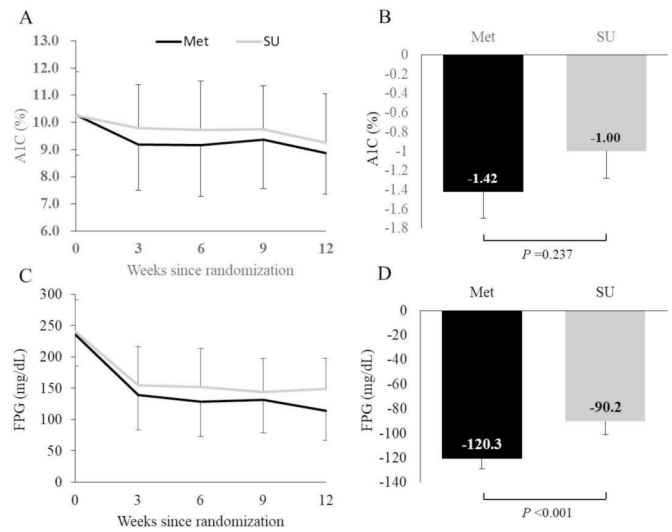


Figure 2. Change in glycosylated hemoglobin (A1C) and fasting plasma glucose (FPG) over 12 months. (A) A1C values from baseline to month 12. (B) Change in A1C values from baseline to month 12. (C) FPG values from baseline to month 12. (D) Change in FPG values from baseline to month 12. Data are mean ± SD or mean ± SE, with last observation carried forward. Met, metformin group; SU, sulfonylurea group.

patients achieving the A1C target displayed no significant differences among the two study groups, mean FPG levels were lower in the Met-group compared to the SU-group, and more proportions of patients in the Met-group achieved the FPG target of < 130 mg/dL than the SU-group. A possible explanation for this is that metformin acts directly or indirectly on the liver to reduce hepatic glucose production and has a better effect on decreasing fasting glucose while the SU achieved a greater reduction in postprandial plasma glucose.¹⁹ Moreover, another reason may be that type 2 diabetes is characterized by declining beta-cell function. Our patients had long diabetes duration and fail to maintain optimal glycemic control with a combination of maximum dose of metformin and a SU, the beta-cell function was reduced and decreased pancreatic beta-cell response to the insulin-stimulating activity of SU. Metformin may enhance insulin sensitivity and therefore has a greater effect on patients with poor beta-cell function.¹⁹

There were only 12.8% (Met-group) and 6.8% (SU-group) patient achieving the A1C target, which was lower than prior studies. This could be probably due to our patient had higher baseline A1C (10.3%) and most of our patients treated with two or three maximal tolerated dosage of OADs. According to the findings of the First Basal Insulin Evaluation Asia study, initiation of insulin was delayed in many Asian countries.²⁰ Previous review showed that there was an inverse relationship between the baseline A1C levels and the number of OADs used by patients at baseline and the likelihood of those patients of achieving glycemic goals.^{17,21} Many patients in our study with an A1C ≥ 7.0% despite having an FPG < 130 mg/dL indicated

that they delayed initiation of insulin and required advancing to combination injectable therapy. In addition, our study design was similar to conditions in actual practice, allowing only five visits during the 48 weeks study period. Even though patients were educated on how to adjust their insulin doses using self-monitored blood glucose data, many patients hesitated to follow the algorithm for adjustment of insulin glargine; and only adjusted the insulin dose after visiting the study site. Previous trials proposed that FPG was significantly lower in those reaching the A1C target than in those who did not;^{10,12} therefore, the higher FPG target and lower rate of patients achieving the FPG target may be important reasons why more patients in our study failed to achieve an A1C of < 7% compared to previous studies. Few studies have evaluated the efficacy of insulin therapy in elderly patients.²² Our post hoc analysis showed there were no significant differences in the reduction of A1C between elderly and non-elderly patients in both groups.

In this study, insulin glargine was initiated at 0.4 IU/kg/day, which was higher than the initiating dose in previous studies and the consensus algorithm for initiation of insulin of guidelines.^{15,16,18} This is because patients were switched from multiple OAD use to a single OAD class in our study, and we anticipated that a higher initiating dose would be required. The final dose of insulin glargine in the present study was 0.62–0.67 IU/kg/day, similar to previous studies (0.42 to 0.78 IU/kg/day).^{6–14} Despite the fact that we started with a higher dose of insulin glargine, the percentage of patients experiencing episodes of symptomatic hypoglycemia were similar to previous studies and there was only one case of major hypoglycemia during the study period.

There were some limitations to this study. Firstly, it was a single-center prospective, open-label study and, therefore, it entailed a risk of bias. Secondly, the study population was relatively small, which allows us to draw statistically supported conclusions only on our primary end point. Finally, we did not include several new classes of OADs, like sodium-glucose cotransporter-2 inhibitors, dipeptidyl peptidase-4 inhibitors or a combination of two classes of OADs. Further studies are required to evaluate which regimen is better when initiating of basal insulin.

5. Conclusion

This 48-week prospective, open-label real-world clinical practice study, conducted on patients with type 2 diabetes mellitus poorly controlled with > 2 OADs; switching to insulin glargine with Met or insulin glargine with SU, showed comparable effectiveness in improving glycemic control.

Conflicts of interest

There are no conflicts of interest.

Source of support

None.

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