

ORIGINAL ARTICLE

Beinagliide, a novel sodium-glucocorticoid cotransporter 2 inhibitor, improves glycaemic control and lipid profile in patients with type 2 diabetes mellitus: a 3-month, placebo-controlled, randomised trial

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Abstract

Aims

The purpose of this study was to examine the effectiveness of beinagliide on body weight, glycaemic haemoglobin (HbA_{1c}), blood pressure and lipid profile in patients with type 2 diabetes mellitus (T2DM) in a real-world setting in China.

Materials and methods

This is a multicentre, observational, retrospective, open-label study conducted in China. Data were collected from T2DM patients who started treatment with beinagliide between 2017 and 2018.

Results

A total of 314 patients were included in the study. After 3 months of treatment with beinagliide, there were significant reductions in body weight (−10.05 kg [95% confidence interval −9.29 to −10.80]), HbA_{1c} (−2.87% [−2.62 to −3.11]), 2-h postprandial plasma glucose (−5.46 mmol L^{−1} [−4.96 to −

increasing aension of their comprehensive effect on both glycaemic control and weight loss in high postprandial glucose incidence.

Beinagide (formerly known as benagide), a GLP-1RA, is a recombinant human glucagon-like peptide-1 and has 100% homology with human GLP-1(7-36) (5). The drug was approved by the China Food and Drug Administration for the treatment of T2DM in December 2016. Beinagide is one of the GLP-1RA recommended for the treatment of T2DM by the Chinese guideline for the prevention and treatment of type 2 diabetes (2017 edition) (6). The efficacy and safety of beinagide have been assessed in randomized controlled trials (RCT) in China (7–9). Similar to other GLP-1RA, beinagide is effective in lowering glycaemic haemoglobin (HbA_{1c}), fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) in patients with T2DM (7,8). In addition, beinagide reduced body weight and body mass index (BMI) in T2DM patients with overweight and obesity (7,9). The RCT provided evidence of the effectiveness of beinagide in a well-defined patient population under a strict controlled environment, especially in certain

of HbA_{1c} reduction and weight loss. Independent variables included age, sex, diabetes duration, baseline HbA_{1c}, BMI, SBP, triglyceride, LDL-C, HDL-C and history of being at risk of type 2 diabetes. $p < 0.05$ was considered statistically significant (two-tailed). Data were analysed using SPSS 23.0 software (IBM SPSS, USA).

Based on the data, the impact on for missing data (i.e. observed data only), a sensitivity analysis was conducted to assess whether the LOCF method for handling missing data might have influenced any critical conclusion.

Results

Baseline characteristics of patients

From January 2017 to March 2018, data from 323 patients treated with being at risk of type 2 diabetes were extracted from the electronic medical record system. Of these, nine patients lacked baseline data for HbA_{1c} and body weight (unknown reason) and were excluded from the analysis. The remaining 314 patients were included in the FAS (see flow chart in Figure 1). There were 163 (51.9%) men and 151 (48.1%) women, with an overall mean age of 47.6 (10.5) years. Most patients (60.3%) had a diabetes duration < 5 years. On average, baseline body weight

was 77.94 (10.91) kg, BMI was 27.95 (4.07) kg m⁻², HbA_{1c} was 9.05 (1.48)%, 2-h PPG was 14.23 (3.23) mmol L⁻¹ and FPG was 9.25 (1.77) mmol L⁻¹. Baseline characteristics of the FAS population are summarised in Table 1. Approximately 27.7% of the FAS population were drug-naïve patients who were newly diagnosed with T2DM. Regarding the history of previous anti-diabetic medication before initiating being at risk of type 2 diabetes, 30.3% of patients had been treated previously with metformin, 14.0% with repaglinide, 12.7% with acarbose, 10.8% with glimepiride, 8.6% with glipizide, 7.0% with basal insulin, 1.9% with DPP4 inhibitor and 1.0% with liraglutide. In addition, 48.1% of patients had received one anti-diabetic agent, 21.0% received two anti-diabetic agents and a small proportion (3.2%) received three anti-diabetic agents prior to being at risk of type 2 diabetes. Regarding diabetic complications, 12.7% and 1.3% of patients presented with a peripheral history of coronary heart disease and brain infarction, respectively. Diabetic peripheral neuropathy, nephropathy and retinopathy were present in 40.4%, 13.7% and 2.2% of patients, respectively. A total of 10.5% of patients presented with both diabetic peripheral neuropathy and nephropathy, and a small proportion (0.1%) presented with diabetic peripheral neuropathy, nephropathy and retinopathy. Hypertension was present in 51.9% of patients, 84.0% of whom

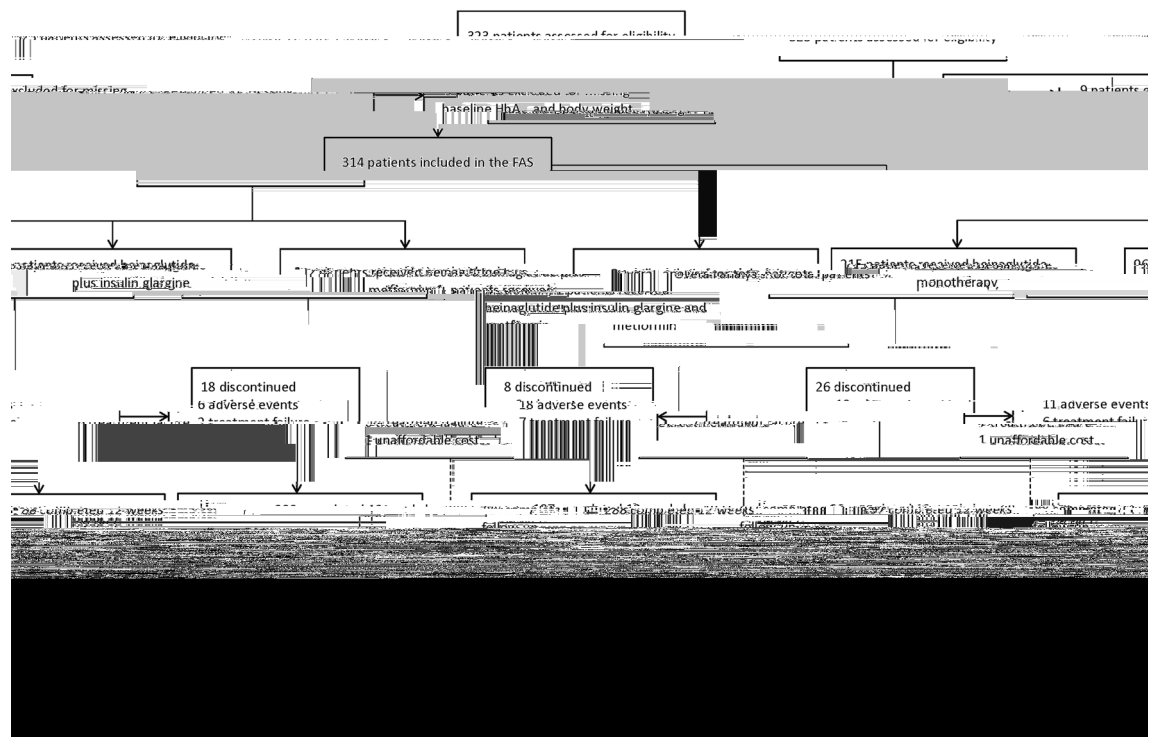


Figure 1 Study flow chart. FAS, full analysis set; HbA_{1c}, glycaemic haemoglobin.

meformin and one (0.3%) in combination with insulin glargine and meformin. At baseline, 37.6% of the patients were prescribed a daily dose of 0.2 mg, 52.3% received 0.3 mg, 5.5% received 0.4 mg, 0.5% received 0.45 mg and 4.1% received 0.6 mg of beinaglide. Following a period of dose escalation of 1–2 weeks, prescription of 0.2, 0.3, 0.4, 0.42, 0.48 and 0.6 mg of beinaglide were given to 31.2%, 5.7%, 2.1%, 11.3%, 22.7% and 27.1% of the patients, respectively. In addition, 96.0% of patients carried out complementary lifestyle interventions.

Clinical outcome after 3 months of beinaglide treatment

Clinical parameters at baseline and the 3-month follow-up are presented in Table 2. Compared with baseline, after 3 months of treatment, the patients showed significant

received an intervention in the treatment. Dyslipidaemia was present in 33.4% of patients, 79.0% of whom received lipid-lowering treatment.

Beinaglide administration

At baseline, 215 patients (68.5%) used beinaglide monotherapy, 96 (30.6%) used beinaglide in combination with insulin glargine, and 0 (0.6%) in combination with

Table 2 Clinical parameters compared in baseline after 3-month treatment

Variable	Total (N = 314)						Subgroup					
	Baseline			After treatment			Baseline			After treatment		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Body weight, kg	266	77.84 (10.70)		187	77.63 (11.19)		187	77.63 (11.19)		67	77.49 (8.28)	
HbA _{1c} , %	208	9.02 (1.53)		134	8.78 (1.36)		134	8.78 (1.36)		73	9.46 (1.72)	
2-h PPG, mmol L ⁻¹	255	14.21 (3.29)		186	14.41 (3.11)		186	14.41 (3.11)		67	13.36 (3.31)	
FPG, mmol L ⁻¹	256	9.24 (1.79)		187	9.11 (1.65)		187	9.11 (1.65)		67	9.42 (1.76)	
C-peptide, nmol L ⁻¹	97	0.98 (0.45)		35	1.13 (0.30)		35	1.13 (0.30)		62	0.89 (0.50)	
BMI, kg m ⁻²	262	27.93 (4.11)		187	27.96 (4.47)		187	27.96 (4.47)		76	27.64 (2.48)	
WC, cm	244	95.84 (14.63)		177	100.20 (13.96)		177	100.20 (13.96)		67	84.37 (9.17)	
Hear rate, bpm	105	76.55 (6.78)		39	73.86 (4.27)		39	73.87 (4.12)		66	76.55 (6.54)	
SBP, mmHg	178	143.60 (19.04)		108	128.50 (8.78)		108	129.60 (8.78)		67	119.04 (19.04)	
<0.0001	0.0001	0.0001	0.0001	<0.0001	0.0001	0.0001	<0.0001	0.0001	0.0001	0.0001	0.0001	0.0001

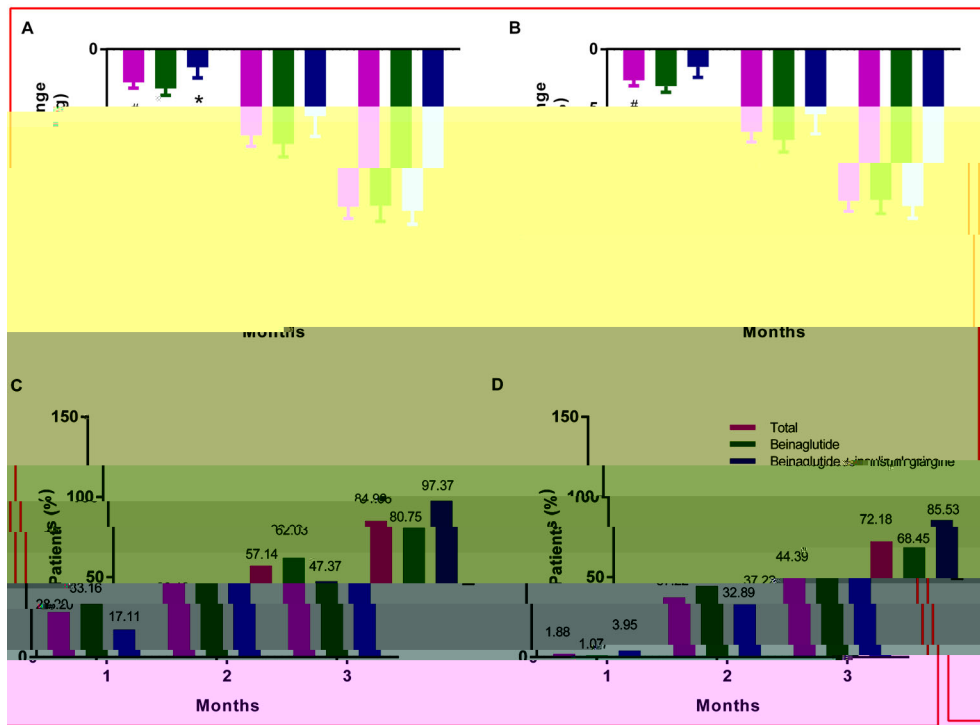


Figure 2 Temporal trend in body weight between baseline and 3 months. (A) Absolute change in body weight (kg). (B) Relative change in body weight (%). (C) The proportion of patients with weight loss of $\geq 5\%$. (D) The proportion of patients with weight loss of $\geq 10\%$. The bar shows the lower limit of 95% CI. Significant change from baseline are indicated (* $p < 0.01$, # $p < 0.0001$). [Correction added on 10 July 2019, after first online publication: Figure 2 has been replaced in this version.]

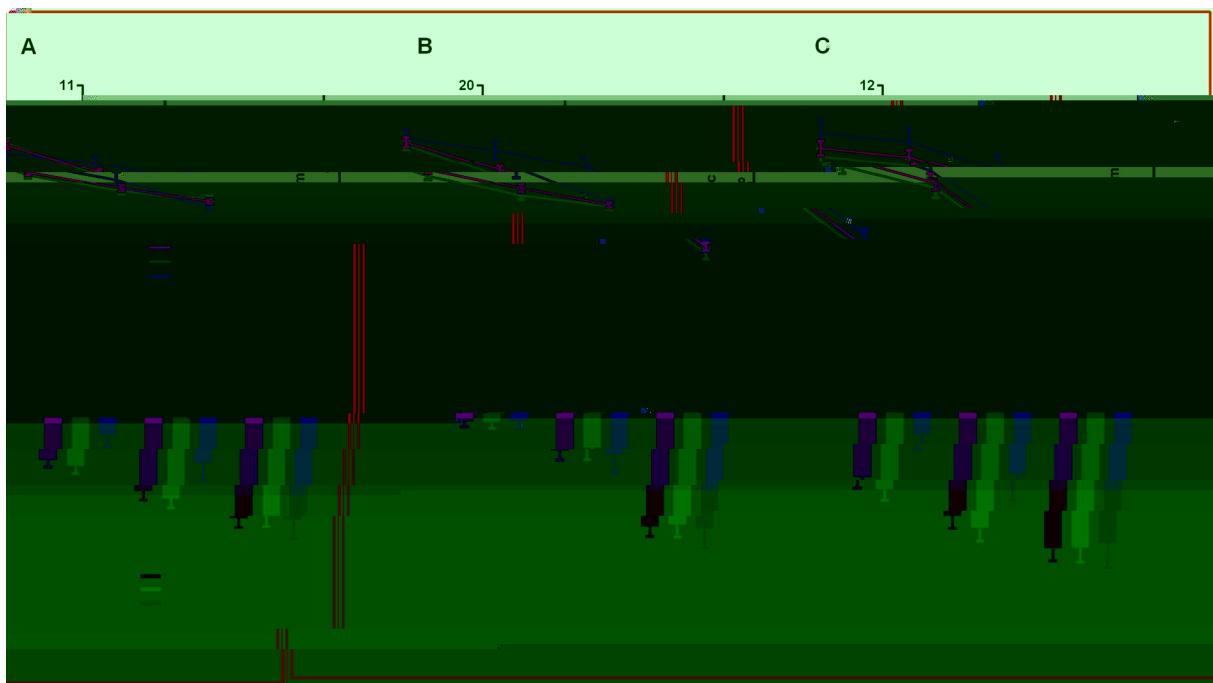


Figure 3 Temporal trend of glycaemic parameters between baseline and 3 months. (A) Mean value of HbA_{1c}. (B) Mean value of PPG. (C) Mean value of FPG. (D) Mean change in HbA_{1c}. (E) Mean change in PPG. (F) Mean change in FPG. The bar shows the lower limit of 95% CI. Significant change from baseline are indicated (* $p < 0.01$, # $p < 0.0001$). FPG, fasting plasma glucose; HbA_{1c}, glycated haemoglobin; PPG, postprandial glucose.

change in 2-h PPG and FPG after 3 months reached $-5.46 \text{ mmol L}^{-1}$ (-4.96 to -5.95) and $-3.04 \text{ mmol L}^{-1}$ (-2.78 to -3.31) (all $p < 0.0001$), respectively. The statistical result of the subgroup showed a similar trend. For patients receiving beinaglide monotherapy, the average change in HbA_{1c} , 2-h PPG and FPG gradually decreased over 3 months and reached -2.83% (-2.53 to -3.12), $-5.44 \text{ mmol L}^{-1}$ (-4.88 to -5.99) and $-2.97 \text{ mmol L}^{-1}$ (-2.67 to -3.27) (all $p < 0.0001$) after 3 months of treatment, respectively. For patients receiving combination therapy with beinaglide and insulin glargine, the average change in HbA_{1c} , 2-h PPG and FPG after 3 months reached -2.94% (-2.49 to -3.39), $-5.24 \text{ mmol L}^{-1}$ (-4.27 to -6.21) and $-3.10 \text{ mmol L}^{-1}$ (-2.55 to -3.64) (all $p < 0.0001$), respectively.

Deailed result (mean difference, standard error and 95% CI) of the temporal trend in HbA_{1c} , 2-h PPG, FPG and body weight are reported in Table S1–S3.

Change in body weight and HbA_{1c} according to baseline characteristics and the dose of beinaglide

The change in body weight did not show significant difference ($p = 0.097$), age ($p = 0.157$), diabetes duration ($p = 0.157$) or baseline HbA_{1c} category ($p = 0.949$). The change in HbA_{1c} also did not show significant difference ($p = 0.471$), age ($p = 0.249$), diabetes duration ($p = 0.169$) or baseline BMI category ($p = 0.964$). However, the change in body weight was significantly greater in patients with $\geq 28 \text{ kg m}^{-2}$ of baseline BMI and in patients receiving beinaglide 0.60 mg ($p = 0.007$ and $p < 0.0001$, respectively); and the change in HbA_{1c} was significantly greater in patients with $\geq 9.0\%$ baseline HbA_{1c} and in patients receiving beinaglide of 0.40 – 0.48 mg (all $p < 0.0001$) (Figure S1).

Determinant of weight loss and HbA_{1c} reduction

The result of multiple linear regression model showed that weight loss from baseline to 3 months positively correlated with baseline BMI level and the dose of beinaglide, and the HbA_{1c} reduction from baseline to 3 months positively correlated with baseline HbA_{1c} level and the dose of beinaglide (Table S4 and S5).

Adverse events, hypoglycaemic events and discontinuation

Among patients in the FAS, the most common adverse events were gastrointestinal symptoms, including nausea (51.0%) and vomiting (18.2%). Other reported adverse events were dizziness (17.2%) and headache (8.3%).

The adverse events mainly occurred in the first month after initiation of treatment, and most were mild to moderate. A total of 14 symptomatic hypoglycaemic events were recorded within the 3 months prior to beinaglide treatment, but no changes were reported after beinaglide treatment. A total of 26 patients (8.3%) discontinued beinaglide therapy within 3 months owing to gastrointestinal adverse effects (5.7%), treatment failure (2.2%) or nonaffordable cost (0.3%).

Sensitivity analysis performed on the completed data using LOCF imputation as a general conclusion in the conclusion of the aforementioned result (data not shown).

Discussion

The present study is the first multicentre, observational, retrospective, open-label analysis of beinaglide effectiveness in T2DM patients, mostly in overweight and obese, in China. The data demonstrated a mean weight loss of 10.05 kg and a mean reduction of 2.87% in HbA_{1c} after 3 months of treatment. The observational confirmed the effectiveness of beinaglide in a real-world setting.

The patients included in the present study represented a general T2DM population in a real-world setting in China. Baseline data indicated that beinaglide therapy was a commonly prescribed for patients with overweight and obese who had a related hyperglycaemia duration. Notably, 27.7% of the patients were newly diagnosed with T2DM, indicating that beinaglide was generally accepted as a second-line treatment.

For Chinese people, a BMI between 24.0 and 27.9 kg m^{-2} is defined as overweight, and a BMI $\geq 28.0 \text{ kg m}^{-2}$ is categorized as obese (10). In the present study, 56.5% of patients were overweight, 41.2% were obese and only 2.3% were normal weight. When analysing the weight-loss effect of beinaglide on the basis of baseline BMI, patients with overweight and obese experienced greater weight-loss effect. This BMI-dependent effect was similar to that in a previous study of liraglutide (11,12). Data for normal weight Chinese patients were not available for identification, making it impossible for this subgroup to be reliable. Similar to other studies of GLP-1RA (13,14), the weight-loss effect of beinaglide was dose-dependent, with the higher dose (0.6 mg) providing the greater weight loss. In addition, baseline age, sex, age and duration had no impact on drug effectiveness with regard to either glycaemic control or weight loss, which is consistent with previous studies of GLP-1RA (11,15).

The mean reduction in HbA_{1c} in this study was higher than mean reduction reported in the previous RCT of

being able, in which mean reduction from baseline be-

Study Design

The authors acknowledge Yale Dean, Ning Ding and Gao Zhao (Shanghai Benemae Pharmaceutical Corporation) for statistical and editorial assistance.

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Conflict of Interest

The authors have declared that they have no conflict of interest associated with this study.

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