



Efficacy and safety of sitagliptin as a third therapeutic agent in the treatment of type 2 diabetes mellitus

Fatemeh Hayati¹, Amjed Hazim², Teguh Haryo Sasongko¹, Gan Siew Hua¹, Wan Mohd Izani Wan Mohamed³, Juhaida Daud⁴, Nik Soriani Yaacob² and Wan Mohamad Wan Bebakar^{3*}

*Correspondence: wanmohd@usm.my



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¹Human Genome Center, School of Medical Science Universiti Sains Malaysia, 16150 Kubang Kerian, Kota Bharu, Kelantan, Malaysia.

²Department of Chemical Pathology, School of Medical Science Universiti Sains Malaysia, 16150 Kubang Kerian, Kota Bharu, Kelantan, Malaysia.

³Department of Medicine, School of Medical Science Universiti Sains Malaysia, 16150 Kubang Kerian, Kota Bharu, Kelantan, Malaysia.

⁴Family Medicine Clinic, School of Medical Science Universiti Sains Malaysia, 16150 Kubang Kerian, Kota Bharu, Kelantan, Malaysia.

Abstract

Background: Information on sitagliptin as a third line agent in combination with other antidiabetic agents is still lacking. This study evaluated the safety and efficacy of sitagliptin as an add-on therapy in type 2 diabetes mellitus (T2DM) patients with poorly controlled glucose control despite receiving an optimum dose of metformin and sulphonylurea.

Method: In a 24-week, non-randomized, open-labeled trial study, T2DM patients (n=93) who were on optimum dosage of metformin and sulphonylurea were additionally treated with 100 mg sitagliptin daily. Primary efficacy end point was assessed by investigating the changes in hemoglobin A1c (HbA1c) and a secondary efficacy end point was assessed by fasting plasma glucose (FPG). Safety was assessed by recording of hypoglycemia, change in body mass index (BMI), blood pressure, lipid profiles high density lipoprotein (HDL), low density lipoprotein (LDL), total cholesterol (Tc) and triglycerides, serum aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), urea, uric acid and creatinine levels.

Result: The mean HbA1c was reduced by 0.41% ($P < 0.007$), and overall, 18.27% of patients achieved an HbA1c goal of $< 7\%$. After 6 months, ALP was reduced by 5.23 ($P = 0.035$) and uric acid was increased by 16.20 $\mu\text{mol/l}$ ($P = 0.048$) respectively. There was no significant change in LDL, Tc, triglycerides, FPG, BMI, blood pressure, urea, AST and ALT. Hypoglycemia was observed only in a small percentage (2.65%) of patients. Although uric acid levels were slightly increased in this study, they were still within the normal range.

Conclusion: Sitagliptin is effective and safe to be used in combination with metformin and sulphonylurea therapies.

Keywords: Diabetes, dipeptidyl peptidase 4 inhibitors, sitagliptin, HbA1c

Introduction

Improvement in glucose control is the most important therapeutic approach in primary prevention of diabetic complications. To date, several oral anti-hyperglycemic drugs are available to induce glucose level to near normalcy. Evidence from the literature has demonstrated that a high percentage (60%) of patients do not achieve glycemic targets due to the progressive nature of type 2 diabetes (T2DM) making combination therapy for optimal glycemic control a necessity [1].

Ensuring optimal efficacy of the drug in mono- or combination therapies during clinical trials is of paramount importance to ensure the safety of patients while giving minimal adverse effects. There are different classes of anti-diabetic drugs, the selection of which is dependent on the type of diabetes, patients and drug characteristics [2]. Thiazolidinedione, glinides, sulphonylurea, pramlintide, metformin and glucagon-like peptide-1 agonists (GLP-1) are beneficial in lowering hemoglobin A1c (HbA1c) but are not without adverse effects [3]. Dipeptidyl peptidase 4

inhibitors (DPP-4 inhibitors) also play a vital role in the treatment of diabetes and have relatively limited adverse effects.

Sitagliptin is an orally active, potent and highly selective DPP-4 inhibitors usually prescribed in a single daily dose. Sitagliptin is approved in many countries for the treatment of patients with T2DM. The safety and efficacy of sitagliptin monotherapy in treating T2DM has previously been well-established [4]. Additionally, the efficacy and safety of sitagliptin have also been established among T2DM patients who do not have adequate glycemic controls with metformin monotherapy [5-17]. However, information on the efficacy and safety of sitagliptin when prescribed as a third line agent in addition to other oral anti hyperglycemic drugs is still lacking. This trial was conducted to determine the benefits of sitagliptin when used in combination with metformin and sulphonylurea by addressing its efficacy and safety.

Materials and methods

Patients

Patients were diagnosed as having T2DM based on the 1998 revised diagnostic criteria established by the World Health Organization Expert Committee (WHO). All were adult patients ageing 18 and above with no history of myocardial infarction or malignancy observed within six months prior to the study. Subjects with HbA1c levels between 7% and 11.5% as well as serum creatinine levels of less than 130 $\mu\text{mol/l}$ were eligible for the trial. Only patients who have not been treated with any type of DPP-4 inhibitor before the trial were recruited. Patients who had a prior history of impaired hepatic function were excluded.

Study design

A prospective, non-randomized, single arm, intervention study design was used. A total of 93 patients were assigned to receive sitagliptin (100 mg daily) in addition to their previous medications (metformin and sulphonylurea). Data collection was conducted before and after 24 weeks of sitagliptin therapy. All patients were enrolled following signed written informed consents. The protocol as well as patient consent forms were approved by the Human Research Ethics Committee, Universiti Sains Malaysia per reference USMCK PPP JEPeM [230.3] [13], prior to study commencement. The study was conducted in accordance with Good Clinical Practice and complies with the Declaration of Helsinki.

Study end points

The primary efficacy end point of this trial was the change in HbA1c values from the baseline. The secondary efficacy end points were changes in fasting plasma glucose (FPG), when compared to baseline.

Safety end points

The data were collected from history, physical and laboratory examination throughout the 24 weeks treatment period.

Laboratory investigations included blood chemistry for urea, uric acid, creatinine, aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP) and lipid profiles. Any clinical adverse events were assessed by investigators for their possible relationships with the study drug. The adverse events of interest included hypoglycemia and gastrointestinal effects such as abdominal pain or discomfort, nausea, vomiting and diarrhea. Mild hypoglycemia is defined as that which is recognized and treated by the patients themselves while severe hypoglycemia is defined as that which patients are unable to self-treat due to impairment of cognitive function. All laboratory measurements were conducted at the Universiti Sains Malaysia (Chemical Pathology and Endocrinology laboratories). The HbA1c levels were analyzed using high performance liquid chromatography (Bio-Rad D-10 analyzer, USA) method. FPG, lipid profiles, AST, ALP, ALT, uric acid were determined using enzymatic methods while urea and serum creatinine were measured using ultraviolet and kinetic colorimetric assay methods respectively.

Statistical analysis

All statistical analyses were conducted using SPSS (Chicago, IL, USA) software version 19.0 for Microsoft Windows[®]. The patients' clinical characteristics were expressed as mean \pm SD. Pre- and post-trial measurements were statistically analyzed using paired sample t-tests. Changes were considered clinically significant when $P < 0.05$.

Results

Patient demographics, baseline disease characteristics and disposition

A total of 800 patients were screened in this study (Figure 1). From this number, 130 fulfilled the inclusion and exclusion criteria out of which 113 were successfully enrolled. During the study, 20 subjects dropped out due to gastrointestinal side effects [2], hypoglycemia [3], headache and dizziness [2], difficulty in passing urine [1], hyponatremia [1] and chest pain [1] while 10 patients failed to follow up. The baseline characteristics

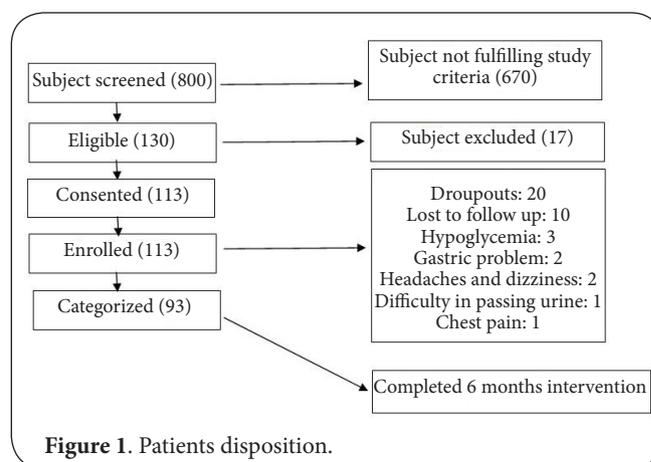


Figure 1. Patients disposition.

of the subjects are summarized in **Table 1**. The majority of subjects received gliclazide and sulphonylurea before and during the study. The dose of metformin and sulphonylurea were maintained throughout the study.

Table 1. Baseline characteristics of all subjects.

Characteristics	Subjects
Male:Female	44:49
Age (yr)	55.55±8.789
Duration of T2DM (yr)	7.52±4.524
SBP (mmHg)	135.31±17.87
DBP (mmHg)	81.49±9.466
BMI (kg/m ²)	29.023±5.117
FPG (mmol/l)	8.872±3.294
HbA1c (%)	8.897±1.30

Data are expressed as means±SD unless otherwise stated. T2DM: Type 2 diabetes mellitus; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BMI: Body mass index; FPG: Fasting plasma glucose; T2DM: Type 2 diabetes mellitus; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BMI: Body mass index; FPG: Fasting plasma glucose

Efficacy

The patients' mean HbA1c levels were significantly decreased following 6 months of treatment with sitagliptin 0.41% ($P<0.007$) (**Table 2**). However, the change in HbA1c levels varied substantially from one patient to another with patients having higher levels of baseline HbA1c (>9%) had greater mean reductions in HbA1c (**Figure 2**). Eighty percent of patients had a reduction of HbA1c to below 7%. At the end of the trial. There was no significant difference between the mean FPG after 6 months when compared to baseline ($p=0.283$).

Body mass index (BMI) and blood pressure (BP)

There was a 0.07 kg/m² decrease in the mean BMI of all subjects

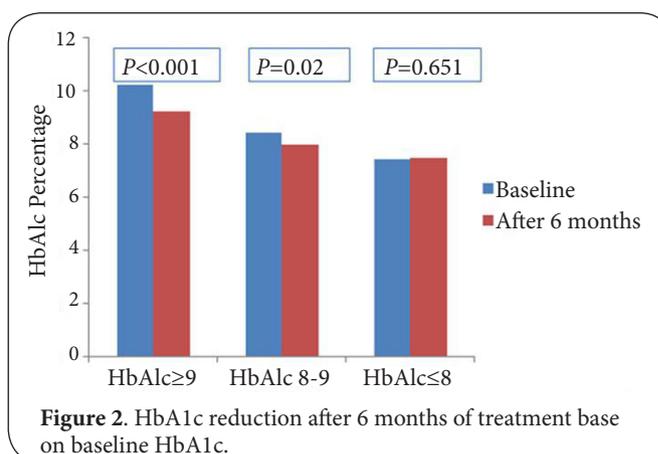


Figure 2. HbA1c reduction after 6 months of treatment based on baseline HbA1c.

at 24 weeks when compared to baseline ($P=0.475$). However, the difference is not statistically significant (**Table 2**). There was also no significant difference between the systolic blood pressure (SBP) ($P=0.2$) and diastolic blood pressure (DBP) ($P=0.907$) at 24 weeks when compared to baseline.

Lipid profiles

After 6 months of sitagliptin therapy, significant changes were observed in mean HDL. No significant change was observed in LDL, triglyceride and total cholesterol levels (**Table 2**).

Safety

Hypoglycemia

Treatment with sitagliptin was generally well-tolerated over the 6 months treatment period. Clinical adverse events were reported in 8.84% of subjects leading to discontinuation of therapy. Mild hypoglycemia, reported in 2.65% of cases, was the most frequently reported adverse event followed by gastric problems (1.76%), headache and dizziness (1.76%), hyponatremia and chest pain (0.88%).

Biochemical parameters

There was no significant difference between ALT, AST, serum

Table 2. Summary of efficacy parameters following 6 months co-therapies with sitagliptin.

Parameters	Baseline	6 months	T statistic (df)	P value
Weight (kg)	73.56±16.474	73.39±16.372	0.595 (92)	0.553
BMI (kg/m ²)	29.018±5.171	28.941±5.109	0.718 (92)	0.475
Systolic BP (mmHg)	135.31±17.876	138.25±21.280	-1.291 (92)	0.2
Diastolic BP (mmHg)	81.49±9.466	81.30±13.160	0.117 (92)	0.907
HDL (mmol/l)	1.234±0.255	1.176±0.248	3.493 (92)	0.001
LDL (mmol/l)	2.848±0.959	2.959±1.117	-1.006 (91)	0.317
Triglyceride (mmol/l)	1.758±1.166	1.904±1.521	-9.860 (92)	0.326
TC (mmol/l)	4.856±1.213	4.931±1.332	-0.597 (92)	0.552
FPG (mmol/l)	8.872±3.294	9.327±3.516	-1.080 (92)	0.283
HbA1C (%)	8.897±1.363	8.480±1.613	2.740 (92)	0.007

P value calculated using paired sample t test

creatinine and urea levels following 6 months of therapy with sitagliptin when compared to baseline (Table 3). Uric acid levels however, showed a slightly significant increase ($P=0.048$) which was still within normal range. The level of ALP was significantly decreased ($P=0.035$) following sitagliptin therapy.

Table 3. Summary of biochemical parameters.

Parameters	Baseline	6 months	T statistic (df)	P value
Creatinine ($\mu\text{mol/l}$)	94.080 \pm 18.189	94.090 \pm 21.9	-0.007 (92)	0.994
Urea (mg/dl)	5.382 \pm 1.562	5.175 \pm 1.983	1.404 (92)	0.164
Uric acid	342.60 \pm 96.810	358.59 \pm 117.759	-2.005 (92)	0.048
AST (u/l)	29.90 \pm 13.539	30.88 \pm 13.187	-0.789 (92)	0.432
ALT (u/l)	43.74 \pm 26.837	43.30 \pm 23.909	0.272 (92)	0.787
ALP (u/l)	93.12 \pm 28.658	88.69 \pm 27.901	2.140 (92)	0.035

Discussion

This study was carried out to determine the efficacy and safety of 100 mg sitagliptin, taken once daily as an add-on therapy, in patients with T2DM whose glucose levels were inadequately controlled despite being on optimum doses of metformin in combination with sulphonylurea were investigated over 6 months of treatment. The study revealed a reduction in mean HbA1C by 0.41% from baseline. Overall, 18.27% patients achieved the American Diabetes Association recommended HbA1c goal of <7.0% [18] after 6 months of therapy. In previous multinational clinical trial of add sitagliptin in combination use with metformin and sulphonylurea [19], patients (n=102) with poorly controlled T2DM on glimepiride and metformin therapy received the addition of 100 mg sitagliptin, once daily for 24 weeks. The -addition of sitagliptin reduced HbA1C by 0.59% from baseline. The higher HbA1c reduction in this study could be due to the higher mean baseline of HbA1c and races different.

In another report [20], eighty-two subjects were sequentially recruited for a 52-week, prospective, single arm study. Sitagliptin was added to low dosage sulphonylurea (glimepiride or gliclazide) with or without metformin for 52 weeks. The change in HbA1c after 52-week treatment was -0.80% (95% CI 0.90 to 0.68) ($p<0.001$). Higher reduction in HbA1c compare to current study could be due to longer duration of study. In current study FPG did not decrease after 6 month of sitagliptin therapy. The fact that DPP-4 inhibitors reduce post prandial blood sugar more effectively than FPG.

DPP-4 inhibitors are also known as body weight-neutral [21]. We observed that there was no significant change in BMI following 6 months sitagliptin therapy ($P=0.475$). This result was consistent with previous study [20].

The HDL has decrease significantly in this study from 1.234 to 1.76 mmol/L ($P=0.001$). We conclude that the decrease of

HDL in this study could be due to the subjects diet which reflect by increasing in TG level.

Sitagliptin is known as a safe drug for both mono and combination therapies. Small percentage (2.65%) of our patients experienced minor hypoglycemia. Among Japanese patients, the incidence of hypoglycemia was reported to be higher 4.28% (3 of 70) in 24 weeks when sitagliptin was added to low dosages of sulphonylurea or sulphonylurea and metformin [20].

ALP was decreased in the present study after 24 weeks of sitagliptin therapy ($P=0.035$). It has been suggested that activation of incretin by sitagliptin can affect the levels of ALP [22]. In current study, we observed only a slight increase in uric acid even though the mean level was still within the normal range.

Conclusion

This study showed that treatment with 100 mg sitagliptin, taken once daily in addition to metformin and sulphonylurea, led to clinically meaningful reductions in HbA1c. Overall, treatment with sitagliptin was well tolerated with low incidence of minor hypoglycemia.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	FH	AH	TS	GS	WWM	JD	NY	WWB
Research concept and design	✓	✓	✓	✓	✓	--	✓	✓
Collection and/or assembly of data	✓	✓	--	--	✓	✓	--	✓
Data analysis and interpretation	✓	--	✓	✓	✓	--	--	✓
Writing the article	✓	--	--	--	--	--	--	--
Critical revision of the article	--	--	✓	✓	✓	--	✓	✓
Final approval of article	--	--	--	--	--	--	--	✓
Statistical analysis	✓	--	--	--	--	--	--	--

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