



This Research Paper is accompanied by Editorial, see page 131.

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# Real World Study of Effectiveness of Gemigliptin Add-On Therapy in Type 2 Diabetes Mellitus

## ABSTRACT

**Background:** Dipeptidyl peptidase-4 (DPP-4) inhibitors are a new class of oral antidiabetic agents that increase endogenous levels of incretin hormones and lead to an increased insulin level and a reduced glucagon level in a glucose-dependent way. Gemigliptin, is a potent, selective, competitive, and long-acting DPP-4 inhibitor. The objective of our study was to evaluate the real-world efficacy and safety of gemigliptin.

**Materials and methods:** A real-world prospective, observational, single-center study conducted in the Endocrinology Department, of a tertiary care hospital. 60 patients were included with 22 (36.7%) female patients. The treatment options consisted of uncontrolled metformin monotherapy, dual combination therapy, triple oral anti-hyperglycemic agents, metformin, and basal insulin combination. Weight, body mass index (BMI), fasting plasma glucose (FPG), 2 hours post prandial glucose (PPG), HbA1c% were documented at baseline and followed up at 3 months.

**Results:** The baseline HbA1c, FPG and PPG were  $9.50 \pm 2.24\%$ ,  $176.71 \pm 67.076$  mg/dL,  $243.37 \pm 93.97$  mg/dl respectively. After 3 months of additional gemigliptin

therapy, HbA1c, FPG, and PPG were significantly reduced to  $8.24 \pm 1.83\%$ ,  $144.32 \pm 50.664$ ,  $184.93 \pm 69.66$  respectively.

**Conclusions:** In real world settings, gemigliptin, a new DPP-4 inhibitor was found to be effective, safe and well tolerated as add-on therapy in adult type 2 diabetes mellitus (T2DM) subjects. (Clin Diabetol 2022, 11; 3: 151-155)

**Keywords:** type 2 diabetes mellitus, DPP-4 inhibitor, gemigliptin

## Research highlights

- Gemigliptin, a new DPP-4 inhibitor was found to be effective as add-on therapy in adult T2DM subjects in real-world settings.
- There was a robust HbA1c (1.25%) reduction with Gemigliptin within 3 months.
- Gemigliptin was found to be safe and well-tolerated as add-on therapy for adult T2DM with a significant reduction in weight and BMI.
- There was no increased risk of adverse effects including hypoglycemia, with add-on gemigliptin therapy in routine clinical practice.

## Introduction

The chronic nature of diabetes mellitus results from the multiple disorders associated with hyperglycemia and dysregulation in the metabolism of fats, proteins,

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and carbohydrates. This results in defects in insulin action and insulin secretion [1]. In 2019, India was home to 77 million individuals with diabetes, ranking second, globally, after China [2]. With over a million diabetes deaths in India, the country remains a huge contributor to regional mortality in South East Asia [3]. These statistics reveal how diabetes is fast gaining the status of a potential epidemic in India and establishes the need for treatment initiatives.

The serine protease enzyme DPP-4 is present all over the body on the cell surfaces [4]. In plasma, the dipeptidyl peptidase-4 (DPP-4) enzyme rapidly inactivates incretins including GLP-1 and GIP which are produced in the intestine depending on the blood glucose level and contribute to the physiological regulation of glucose homeostasis [5]. It is well known that glucose-lowering effects of DPP-4 inhibitors are mainly mediated by GLP-1 and gastric inhibitory polypeptide (GIP) incretin hormones which are inactivated by DPP-4 [5]. DPP-4 inhibitors lead to an increased insulin level and a reduced glucagon level in a glucose-dependent way [5].

Gemigliptin, previously identified as LC15-0444, is a new oral anti-hyperglycemic agent of the dipeptidyl peptidase-4 (DPP-4) class of drugs [6]. Being a reversible, selective, potent, and a long-acting DPP-4 inhibitor, Gemigliptin also has high selectivity over other significant human protease enzymes such as elastase, trypsin, urokinase, DPP-2, DPP-8, DPP-9, and cathepsin G [6]. The DPP-4 inhibition kinetics by gemigliptin was associated with rapid attachment followed by a slow dissociation compared to vildagliptin and sitagliptin [7].

The animal studies on gemigliptin show a half-life of 3.6 h, 5.2 h, and 5.4 h in rats, dogs, and monkeys, respectively, and shown to be rapidly absorbed after single oral dosing. Thus it can be seen that gemigliptin bioavailability could be species dependent [7]. It was also seen that about 80% inhibition of plasma DPP-4 activity was observed at the plasma levels of 18nM, 14 nM, and 4 nM, in studies in rats, dogs, and monkeys respectively [7]. Studies on animals suggest its positive effect on hepatic and renal fibrosis [7].

Gemigliptin is orally administered 50 mg once daily with or without food, either as monotherapy or in combination with other drugs. The reason for no dose adjustment of gemigliptin in moderate to severe renal impairment patients is the balanced process of hepatic metabolism and urinary fecal excretion [8]. Another property of gemigliptin is the low risks of drug interactions with other anti-diabetic drugs such as metformin, pioglitazone, glimepiride, and even lipid-lowering drugs like CYP3A4 inhibitors, rosuvastatin, or irbesartan. Thus, there is no requirement of dose adjustment of gemigliptin in patients who are concomitantly receiving these drugs [8].

The HbA1c reduction of gemigliptin by 1.24% in monotherapy and 0.8% in add-on therapy with metformin proves the efficacy of the drug and it is also reported that gemigliptin is usually well tolerated in controlled clinical studies as part of combination therapy and even as monotherapy. However, there is no Indian real-world clinical data on Gemigliptin, to date. The objective of our study was to evaluate the real-world efficacy and safety of gemigliptin.

## Materials and methods

This was a prospective observational study conducted in the Endocrinology Department at AMRI Hospital, Dhakuria, Kolkata, India. The study was approved by the Independent Ethics Committee of AMRI Hospitals. Patient data were analyzed from July 2016 to March 2017. A total of 60 adults with diabetes mellitus type 2 (T2DM) were enrolled in the study. Inclusion criteria were adults more than 18 years with T2DM patients with inadequate glycemic control (HbA1c > 7%) on metformin alone or combination with metformin and other medications.

Patients who had signed informed consent were included. Exclusion criteria included patients who had been administered gemigliptin prior to the study period, patients with type 1 diabetes or diabetic ketoacidosis, patients with a history of serious hypersensitive reactions, such as anaphylaxis or angioedema to another dipeptidyl peptidase-4 (DPP-4) inhibitor, breastfeeding and pregnant women, patients who had not signed informed consent.

Patient data were collected at baseline and followed up at 3 months. Weight, BMI, fasting plasma glucose (FPG), 2 hours post prandial glucose (PPG), HbA1c% were documented at baseline and followed up at 3 months. Information of all adverse events that occurred during the study period was documented.

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on mean  $\pm$  SD and results on categorical measurements are presented in number (%). Significance is assessed at a level of 5%. Normality of data tested by Anderson Darling test, Shapiro-Wilk, Kolmogorov-Smirnov test and visually by QQ plot. paired t-test has been used to find the significance of study parameters between the same groups of patients for before and after measurement. The Statistical software namely SAS 9.2, SPSS 21.0 were used for the analysis of the data, and Microsoft Word and Excel have been used to generate graphs, tables, etc.

## Results

Sixty patients with adequate follow-up data were included in our study, with 22 (36.7%) female patients. The

**Table 1. Patient Demographics and Baseline Characteristics**

| Parameters                              | Number of patients<br>(n = 60) |
|---|--------------------------------|
| Age [years], (n = 60)                   | 52.2 (35.0–66.0)               |
| Age group [years], n (%)                |                                |
| ≥ 60 – ≤ 40                             | 4 (6.5)                        |
| > 41 – ≤ 50                             | 24 (38.7)                      |
| > 51 – ≤ 60                             | 20 (32.3)                      |
| > 60                                    | 12 (19.4)                      |
| Sex, n (%) (n = 60)                     |                                |
| Men                                     | 38 (63.3)                      |
| Women                                   | 22 (36.7)                      |
| Duration of DM, in years (mean, SD)     | 8.6 ± 1.92                     |
| Biochemical investigations              |                                |
| FPG (mg/dL)                             | 176.71 ± 67.076                |
| PPG (mg/dL)                             | 243.37 ± 93.97                 |
| HbA1c (%)                               | 9.50 ± 2.24                    |
| Serum creatinine (mg/dL),<br>[n = 1258] | 0.7871 ± 0.059<br>(0.64–0.92)  |

**Table 2. Ongoing Anti-Diabetic Medications in Patients**

| Ongoing Anti-diabetic medications   | Number of subjects<br>(%) |
|-------------------------------------|---------------------------|
| Glimepiride + Metformin combination | 14 (22.6)                 |
| Glimepiride + Metformin + Voglibose | 2 (3.2)                   |
| Metformin monotherapy               | 40 (64.6)                 |
| Metformin + basal insulin           | 2 (3.2)                   |
| Metformin + Voglibose               | 2 (3.2)                   |

median age of the study subjects was 52.5 years (range: 35–66 years). Patient demographics and baseline characteristics are shown in Table 1. 56 (90.3%) study subjects had no previous history of liver disease, 2 patients (3.2%) had fatty liver, 2 patients (3.2%) had the previous history of resolved viral A hepatitis 8 years ago. All patients had normal liver function. None of the patients had a history of previous cardiovascular disease (CVD) while 12 (19.3%) patients had a family history of CVD. 42 patients (67.7%) had no addiction, 8 (12.9%) patients were current smoker, 4 (6.4%) patients were ex-smokers.

Table 2 details the ongoing anti-diabetic medications taken by the subjects. 40 (64.6%) patients were uncontrolled on metformin monotherapy, 16 patients were on dual combination therapy, 14 (22.6%) patients were on glimepiride + metformin combination, 2 (3.2%) patients on metformin + voglibose combination. 2 (3.2%) patient was on triple oral anti-hyperglycemic agents glimepiride+metformin+voglibose

combination, 2 (3.2%) patient was on metformin and basal insulin combination (Tab. 2). The maximum dose of glimepiride used was 4 mg.

The baseline HbA1c was  $9.50 \pm 2.24$  % which was significantly reduced after 3 months of gemigliptin to  $8.24 \pm 1.83$ %,  $p < 0.001$ . There was significant ( $p < 0.001$ ) paired difference in HbA1c from baseline: 1.25% (95% Confidence Interval {CI} of the Difference: Lower limit — 0.9211–Upper limit 1.592). 17 (56.7%) subjects achieved HbA1c target of  $\leq 7\%$  at the end of 3 months of study period. The baseline FPG was  $176.71 \pm 67.076$  mg/dL which was significantly reduced after 3 months of gemigliptin to  $144.32 \pm 50.664$ ,  $p < 0.001$ . There was significant ( $p < 0.001$ ) paired difference from baseline in FPG: 32.393 mg/dL (95% CI of Difference: Lower limit — 18.252 mg/dL — Upper limit — 46.533 mg/dL). The baseline 2 hours PPG) was  $243.37 \pm 93.97$  mg/dL which was significantly reduced after 3 months of gemigliptin to  $184.93 \pm 69.66$ ,  $p < 0.001$ . There was significant ( $p < 0.001$ ) paired difference in PPG from baseline: 58.444 mg/dL (95% CI of Difference: Lower limit — 37.763 mg/dL — Upper limit 79.126 mg/dL).

The baseline weight was  $72.77 \pm 12.85$  kg which was significantly reduced after 3 months of gemigliptin to  $71.43 \pm 11.28$  kg,  $p = 0.005$ . The baseline BMI was  $27.90 \pm 4.656$  which was significantly reduced after 3 months of gemigliptin to  $27.43 \pm 4.224$ ,  $p = 0.011$ . There was significant ( $p < 0.011$ ) paired difference in BMI from baseline: 0.467 (95% CI of Difference: Lower limit: 0.117 — Upper limit: 0.817). In the 12 weeks study duration, none of the study patients required rescue medications when gemigliptin was used as an add-on therapy to the existing OADs.

There was no episode of documented or symptomatic or severe hypoglycemia with additional gemigliptin within the 3 months of the study period. One patient had an episode of nasopharyngitis. There were no complaints of headache, nausea, heart failure, hypersensitivity skin reactions, joint pain.

## Discussion

The current real-world study included 60 patients (36.7% female with a median age of 52.5 years) with uncontrolled T2DM who were prescribed gemigliptin 50 mg once daily in addition to current therapy. The baseline HbA1c, FPG and PPG were  $9.50 \pm 2.24$  %,  $176.71 \pm 67.076$  mg/dL,  $243.37 \pm 93.97$  mg/dL respectively. After 3 months of additional gemigliptin therapy, HbA1c, FPG, and PPG were significantly reduced to  $8.24 \pm 1.83$ %,  $144.32 \pm 50.664$ ,  $184.93 \pm 69.66$  respectively. Previous randomized controlled trials have shown that gemigliptin is effective and well-tolerated in T2DM patients. A 24-week, multicenter, multinational,

randomized, double-blind, placebo-controlled phase 3 in 182 patients (74 from Korea and 108 from India), showed efficacy and safety of gemigliptin (50 mg once daily) as monotherapy in T2DM patients. After 24 weeks of gemigliptin treatment, HbA1c was significantly reduced compared to placebo (adjusted mean after subtracting placebo effect size:  $-0.71\%$ , 95% CI:  $-1.04$  to  $-0.37\%$ ). A significantly greater proportion of patients achieved an HbA1c  $< 7\%$  with gemigliptin than with placebo (43 vs. 18%), with similar incidence rates for adverse events. At week 24, gemigliptin showed 19.80 mg/dL of mean placebo-subtracted FPG reduction. In the current study, gemigliptin reduced FPG by 32.393 mg/dL (95% CI:  $-46.533$  to  $-18.252$  mg/dL) and PPG by 58.444 mg/dL (95% CI:  $-79.126$  to  $-37.763$  mg/dL).

In a study involving 425 Asian patients, it was demonstrated that gemigliptin was efficacious and well-tolerated in patients with uncontrolled T2DM on metformin monotherapy, as compared to sitagliptin [10]. At 24 weeks, HbA1c reduction with gemigliptin ( $-0.77\% \pm 0.8$ ) was non-inferior to that caused by sitagliptin ( $-0.8\% \pm 0.85$ ). Proportion of patients achieving HbA1c  $< 7\%$  with gemigliptin (54.07%) was comparable to sitagliptin (48.87%) [10]. The results in Indian T2DM patients were similar to the overall study population ( $-0.83\%$  HbA1c reduction with gemigliptin vs.  $-0.6\%$  with sitagliptin) [10]. Patients in the gemigliptin group had greater inhibition of plasma DPP-4 compared to sitagliptin [10]. There was no increased risk of adverse effects with gemigliptin compared with sitagliptin [10]. This study was extended by 28 weeks in which patients who had been treated with sitagliptin were switched over to gemigliptin, and so all T2DM subjects received 50 mg gemigliptin daily for 28 weeks [11]. HbA1c reduction from baseline was  $-1.06$  in subjects who continued to receive gemigliptin while an additional 0.1% HbA1c reduction from baseline was noted in patients who were switched from sitagliptin to gemigliptin [11]. Thus the addition of gemigliptin to metformin was found to be efficacious for 52 weeks [11]. Switching from sitagliptin 100 mg to gemigliptin 50 mg showed sustained glycemic control in T2DM patients [11]. In another double-blind, placebo-controlled trial, gemigliptin significantly improved glycemic control in T2DM patients inadequately controlled with metformin and sulphonylureas (HbA1c 7–11%) [12]. At 24 weeks, adjusted mean change in HbA1c was  $-0.87\%$  (95% CI  $-1.09\%$  to  $-0.64\%$ ) in the gemigliptin group compared to placebo, from a baseline HbA1c of 8.2% in both groups [12]. Higher proportion of subjects achieved HbA1c of  $< 7\%$  (39.3% vs. 5.5%;  $p < 0.001$ ) with gemigliptin than with placebo, however, the incidence of hypoglycemia was higher (9.4% vs. 2.7%) with

additional gemigliptin therapy [12]. In a multicenter, randomized, active-controlled, open-label exploratory 12-week study, gemigliptin and sitagliptin were more effective than glimepiride in reducing glycemic variability especially mean amplitude of glycemic excursion (MAGE) as initial combination therapy with metformin in patients with type 2 diabetes [13]. The standard deviation (SD) of glucose was significantly lower in patients who received gemigliptin than that in patients who received sitagliptin or glimepiride [13]. In our study, at baseline 40 (64.6%) patients were uncontrolled on metformin monotherapy, 16 (25.8%) patients were on metformin and glimepiride-based therapy. In the present real-world study addition of gemigliptin 50 mg daily significantly decreased, mean HbA1c by 1.25% (95% Confidence Interval:  $-1.592$  to  $-0.9211\%$ ), with 34 (56.7%) of our T2DM subjects achieving HbA1c target of  $\leq 7\%$ . Linagliptin treatment was found to have a more pronounced HbA1c lowering in Japanese and Asian (non-Japanese) patients [14]. T2DM patients of Asiatic origin respond better to gliptin therapy increased in the Indian T2DM patients [15]. This can be due to higher postprandial hyperglycemia due to a high carbohydrate diet and gliptins having better control on postprandial hyperglycemia and glycemic variability. Moreover, plasma DPP4 activity is significantly increased in Asian/ Indian T2DM patients [16, 17]. Circulating CD4 T cells, especially Th17 cells, shed cleaved DPP4 protein into plasma due to the enzymatic action of KLK5 [17]. Expression and secretion of KLK5 are increased in CD4 T cells of Indian T2DM patients [17].

In a pooled safety analysis of one thousand eighty patients, gemigliptin demonstrated good tolerability with both monotherapy and combination therapy [6]. Upper respiratory tract infection, specifically nasopharyngitis, was the most common adverse effect seen in 5% of patients [6]. Gemigliptin therapy did not increase body weight while hypoglycemia incidence was similar to placebo [6]. In the current study, there was no increased risk of adverse effects including hypoglycemia, with add-on gemigliptin therapy. One of our patients had an episode of nasopharyngitis. In our study, baseline weight and BMI ( $72.77 \pm 12.85$  kg and  $27.90 \pm 4.656$  respectively) were significantly reduced ( $71.43 \pm 11.28$  kg and  $27.43 \pm 4.224$  respectively).

The limitations of our study were a small number of patients and short follow-up. However this real-world data in day-to-day clinical practice compliments randomized trial evidence generated under stringent conditions.

## Conclusions

In the current real-world study, gemigliptin was found to be effective, safe, and well-tolerated as add-

on therapy for adult T2DM subjects. There was robust HbA1c (1.25%) reduction without any increased risk of adverse effects including hypoglycemia, with add-on gemigliptin therapy in routine clinical practice.

### Conflict of interest

None declared.

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