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Original Article

A Pharmacokinetic Associative Correlational Study of Varying Drug Doses with Gemigliptin Safety and Antidiabetic Pharmacotherapeutic Compliance

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Abstract

Introduction: Gemigliptin-like anti-dipeptidyl peptidase-4 hypoglycemic drugs cause beta-cell function acceleration by ameliorating the anti-beta-cell apoptotic serum incretins, such as glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide.

Objectives: The objective of this study was to conduct a pharmacokinetic associative correlational study of varying drug doses with gemigliptin safety and antidiabetic pharmacotherapeutic compliance.

Materials and Methods: In this study, 100 new type II diabetes mellitus patients, of early grade, were prescribed oral 25 mg gemigliptin once daily, for 30 days, and then 50 mg gemigliptin once daily, for the next 30 days, in monotherapy, or in combination therapy, or in a mixed regimen of monotherapy and combination therapy, with another oral hypoglycemic agent. The safety assessment was done by the monitoring of adverse drug reactions, such as nasopharyngitis, hypoglycemia, gastrointestinal disturbances, headache, nausea, rashes, urticaria, edema, and weakness, with Adverse Event Case Report Forms, on days 0, 30, 60, and further follow-ups. The analysis of different attributes of patient compliance was performed.

Results: In this study, there was the absence of any significant occurrence of adverse effects, on days 0, 30, 60, and further follow-ups, with increasing doses of gemigliptin therapy. The analyses of the different patient compliance attributes, on days 0, 30, 60, and further follow-ups, showed that the patient compliance was significantly high, throughout.

Conclusions: Gemigliptin was safe and tolerable, with increasing drug doses, and there was high pharmacotherapeutic patient compliance.

Key words: Associative correlation, Gemigliptin, Patient compliance, Pharmacokinetics, Pharmacovigilance, Varying drug doses

INTRODUCTION

Diabetes mellitus type II (T2D), a chronic life-long multisystem endocrinometabolic disorder, has experienced a steep global upsurge, in these contemporary times. An early decrease in beta-cell function, resulting in high postprandial blood glucose, and the development of chronic diabetic complications at an early stage, are the most significant clinical endocrinological differences of T2D between the Asian and the global non-Asian populations. Therefore, the inclusion of an endocrinological pharmacotherapeutic agent, which increases the beta-cell function, seems to be the most essential requirement of an antihyperglycemic regimen. To achieve glycemic targets, the synergistic combination therapies are often preferred, for improvising the

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comprehensive treatment of T2D, with accompanying complications.[1,2]

In accordance with the guidelines of diabetes associations, gemigliptin-like anti-dipeptidyl peptidase-4 (DPP-4) hypoglycemic drugs are being quite extensively used as one of the effective antidiabetic therapeutic agents, which cause augmented beta-cell function by ameliorating the anti-beta-cell apoptotic serum incretins, such as, glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide. DPP-4 inhibitors are the most prevailing incretin-related therapies for T2D diabetics.[2]

Objectives

The objective of this study was to conduct a pharmacokinetic associative correlational study of varying drug doses with gemigliptin safety and antidiabetic pharmacotherapeutic compliance.

MATERIALS AND METHODS

Ethical Approval

At first, the Institutional Ethics Committee clearance and approval was taken. The study was conducted in accordance with the ethical principles of Declaration of Helsinki and Good Clinical Practices contained within the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH-E6 and ICH-E17) and in compliance with the global regulatory requirements. An informed consent was obtained from each patient.

Selection Criteria of the Patients

Inclusion criteria

The inclusion criteria are as follows: (i) Patients of any gender, (ii) patients within 35 and 60 years, (iii) patients presenting with new T2D of early grade, (iv) T2D American Diabetes Association diagnosis criteria, (v) cooperative and conscious patients, (vi) patients willing to undergo all pre- and post-treatment investigations and willing to complete the entire course of treatment, (vii) patients who have given consent and are willing to go for a follow-up, (viii) patients not taking any previous antidiabetic drug, and (ix) patients not taking any concomitant medication.

Exclusion criteria

The exclusion criteria are as follows: (i) Uncooperative or unconscious patients, (ii) patients below 35 and above 60 years, (iii) patients presenting with any grade other than moderate grade of diabetes, (iv) patients with a history of hypersensitivity to any of the study drugs, (v) patients with high-risk diseases or comorbidities, (vi) cardiac, renal, or any other associated complications or comorbidities, (vii) any chronic disease intervening with the study data, (viii) pregnant or lactating women, (ix) pediatric or geriatric patients, (x) other associated medical illness or disorders, like urogenital tract infections, having impact on study results, and (xi) female patients using hormonal contraceptives.

Study Design

The study design was a multicenter, prospective, randomized, open-labeled study.

Study Population

The study population was 100 new early grade T2D patients.

Study Period

The study period was 9 months, from November 2020 to February 2021 and July 2021 to January 2022.

Place of Study

The research study and the compilation of the study literature were conducted in the Departments of Pharmacology, Clinical Pharmacology, Molecular Pharmacology, Rational Pharmacotherapeutics, Pharmacovigilance, Pharmacogenomics, Internal Medicine, Endocrinology, Diabetology, Pathology, Clinical Pathology, Molecular Diagnostics, and Medical Education, in Dr. Moumita Hazra's Polyclinic And Diagnostic Centre, Hazra Nursing Home, Rama Medical College Hospital and Research Centre, Mamata Medical College and Hospitals, and J.J.M. Medical College and Hospitals.

Study Procedure

In this study, 100 new T2D patients, of early grade, were prescribed oral 25 mg gemigliptin once daily, for 30 days, and then 50 mg gemigliptin once daily, for the next 30 days, in monotherapy, or in combination therapy, or in a mixed regimen of monotherapy and combination therapy, with another oral hypoglycemic agent.

The patients' characteristics, diabetic symptoms assessment, patients' disease, and disease-related history were recorded with a study pro forma. Then, thorough general physical examination and systemic examination were performed on the patients under study. The relevant blood, urine, and other investigations were done to confirm the progressing health status of the patients being treated.

The efficacy assessment was done, by recording the fasting and the post-prandial blood sugar level, HbA1c level, and urine routine examination findings including sugar and albumin levels and microscopy, after gemigliptin therapy.

The safety assessment was done by the monitoring of adverse drug reactions, such as nasopharyngitis, hypoglycemia, gastrointestinal disturbances, headache,

nausea, rashes, urticaria, edema, and weakness, with Adverse Event Case Report Forms, (i) on day 0, (ii) on day 30 (for any adverse effect between day 0 and day 30), (iii) on day 60 (for any adverse effect between day 30 and day 60), and (iv) on further follow-ups, after the administration of oral 25 mg gemigliptin once daily, for 30 days, and then 50 mg gemigliptin once daily, for the next 30 days, in monotherapy, or in combination therapy, or in a mixed regimen of monotherapy and combination therapy, with another oral hypoglycemic agent.

The antidiabetic pharmacotherapeutic compliance of the patients, correlated to the occurrence of adverse effects, was thoroughly analyzed, with adequate consideration of causality assessment, conducted by the varied types of patients' responses to any adverse effect occurring, due to the oral administration of gemigliptin in varying doses of 25 mg once daily, for 30 days, and then 50 mg once daily, for the next 30 days, in monotherapy, combination therapy, or mixed regimen of monotherapy and combination therapy. The analysis of the different attributes of patient compliance was performed, by deducing the total number of patients (a) who had participated in the study, (b) who had completed the study thoroughly, (c) who had achieved safe and adequate glycemic control with gemigliptin monotherapy, combination therapy, or mixed regimen of monotherapy and combination therapy, (d) who were lost to follow-up due to unknown causality, (e) who had dropped out due to mild adverse effects, (f) who had dropped out due to moderate adverse effects, (g) who had dropped out due to severe adverse effects, or (h) who had withdrawn voluntarily due to the probability of occurrence of any potential adverse effect, analyzed on (i) day 0, (ii) day 30 (for patient compliance between day 0 and day 30), (iii) day 60 (for patient compliance between day 30 and day 60), and (iv) on further follow-ups.

Statistical Analysis

At the study completion point, the observations recorded in this study were statistically analyzed by Z test, and test of significance with p values, with subsequent tabular representations. The patient compliance assessment was performed by different types of statistical analyses in percentages. These research study results were further displayed by graphical illustrations.

RESULTS

The demographic characteristics of the patients were comparable. As depicted in Table 1, among the 100 new T2D patients, of early moderate grade, receiving oral 25 mg gemigliptin once daily, for 30 days, and then 50 mg gemigliptin once daily, for the next 30 days, in monotherapy, or in combination therapy, or in a mixed regimen of monotherapy and combination therapy, there was the absence of any significant symptomatic observation of the different adverse effect-like attributes, such as nasopharyngitis, hypoglycemia, gastrointestinal disturbances, headache, nausea, rashes, urticaria, edema, and weakness, as observed on day 0. Thus, there was the absence of any previously occurred adverse effect-like symptom, among the patients, which indicate the absence of any causal association of the occurrence of any adverse effect-like symptom related to any previously existing factor, other than the drug gemigliptin. As depicted in Figure 1, the analysis of the different attributes of patient compliance showed that the total number of patients (a) who had participated in the study was 100, (b) who had completed the study thoroughly was 100, (c) who had achieved safe and adequate glycemic control with gemigliptin monotherapy, combination therapy, or mixed regimen of monotherapy and combination therapy was 100, (d) who were lost to follow-up due to unknown causality was 0, (e) who had dropped out due to mild adverse effects was 0, (f) who had dropped out due to moderate adverse effects was 0, (g) who had dropped out due to severe adverse effects was 0, or (h) who had withdrawn voluntarily due to the probability of occurrence of any potential adverse effect was 0. Therefore, the patient compliance was significantly high, on day 0.

Table 1: Day 0: The occurrence of adverse effects or any previously occurred adverse effect-like symptoms on oral 25 mg gemigliptin monotherapy, combination therapy, or mixed regimen of monotherapy and combination therapy

Adverse effects or any previously occurred adverse effect-like symptoms on day 0	Number of patient occurrence with 25 mg gemigliptin	Z value	*P*-value
Nasopharyngitis	0	-	Non-significant
Hypoglycemia	0	-	Non-significant
Gastrointestinal disturbances	0	-	Non-significant
Headache	0	-	Non-significant
Nausea	0	-	Non-significant
Rashes	0	-	Non-significant
Urticaria	0	-	Non-significant
Edema	0	-	Non-significant
Weakness	0	-	Non-significant

As depicted in Table 2, there was the absence of any significant occurrence of adverse effects, such as nasopharyngitis, hypoglycemia, gastrointestinal disturbances, headache, nausea, rashes, urticaria, edema, and weakness, on day 30 (occurrence of adverse effects between day 0 and day 30), after the oral administration of 25 mg gemigliptin monotherapy, combination therapy, and mixed regimen of monotherapy and combination therapy.

As depicted in Figure 2, the analysis of the different attributes of patient compliance, on day 30, showed that the total number of patients (a) who had participated in the study was 100, (b) who had completed the study thoroughly was 100, (c) who had achieved safe and adequate glycemic control with gemigliptin monotherapy, combination therapy, or mixed regimen of monotherapy and combination therapy was 100, (d) who were lost to follow-up due to unknown causality was 0, (e) who had dropped out due to mild adverse effects was 0, (f) who had dropped out due to moderate adverse effects was 0, (g) who had dropped out due to severe adverse effects was 0, or (h) who had withdrawn voluntarily due to the probability of occurrence of any potential adverse effect was 0. Therefore, the patient compliance was significantly high, on day 30 (patient compliance between day 0 and day 30).

As depicted in Table 3, there was the absence of any significant occurrence of adverse effects, such as nasopharyngitis, hypoglycemia, gastrointestinal disturbances, headache, nausea, rashes, urticaria, edema, and weakness, on day 60 (occurrence of adverse effects between day 30 and day 60), after the oral administration of 50 mg gemigliptin monotherapy, combination therapy, and mixed regimen of monotherapy and combination therapy. As depicted in Figure 3, the analysis of the different attributes of patient compliance, on day 60, showed that the total number of patients (a) who had participated in the study was 100, (b) who had completed the study thoroughly was 100, (c) who had achieved safe and adequate glycemic control with gemigliptin monotherapy, combination therapy, or mixed regimen of monotherapy and combination therapy was 100, (d) who were lost to follow-up due to unknown causality was

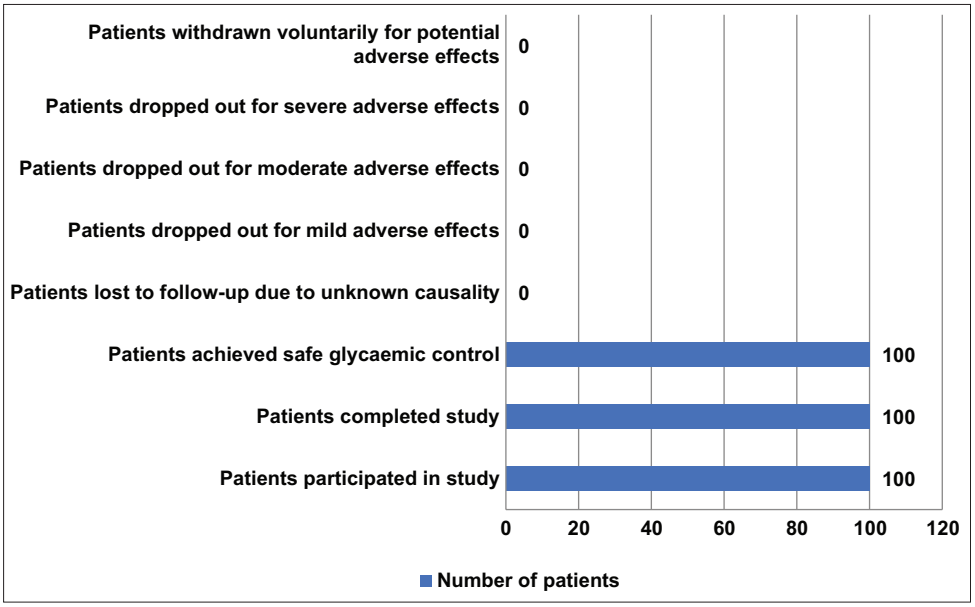

Figure 1: Day 0: Patients' antidiabetic pharmacotherapeutic compliance for gemigliptin therapy

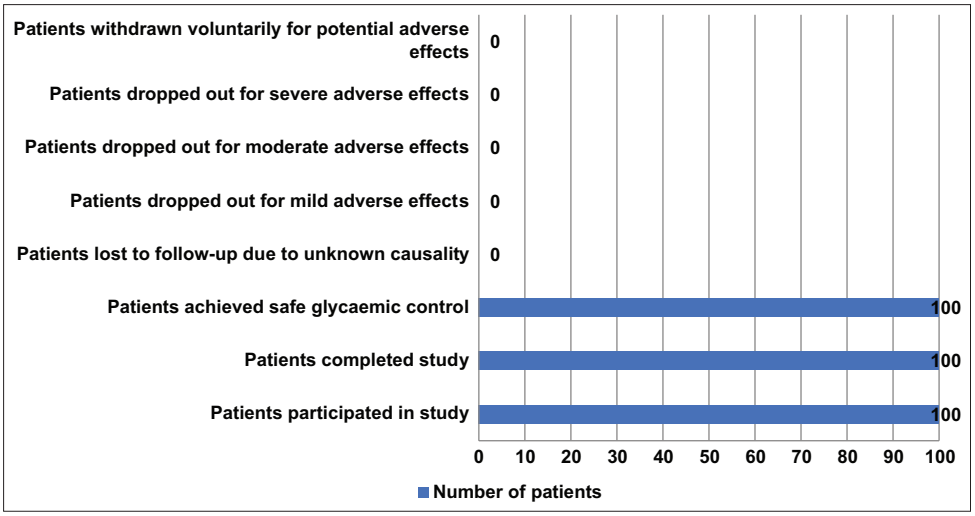

Figure 2: Day 30: Patients' antidiabetic pharmacotherapeutic compliance for gemigliptin therapy

0, (e) who had dropped out due to mild adverse effects was 0, (f) who had dropped out due to moderate adverse effects was 0, (g) who had dropped out due to severe adverse effects was 0, or (h) who had withdrawn voluntarily due to the probability of occurrence of any potential adverse effect was 0. Therefore, the patient compliance was significantly high, on day 60 (patient compliance between day 30 and day 60).

As depicted in Table 4, there was the absence of any significant occurrence of adverse effects, such as nasopharyngitis, hypoglycemia, gastrointestinal disturbances, headache, nausea, rashes, urticaria, edema, and weakness, on further follow-ups (occurrence of adverse effects after day 60), after the oral administration of 50 mg gemigliptin monotherapy, combination therapy, and mixed regimen of monotherapy and combination therapy. As depicted in Figure 4, the analysis of the different attributes of patient compliance, on further follow-ups, showed that the total number of patients (a) who had participated in the study was 100, (b) who had completed the study thoroughly was 100, (c) who had achieved safe and adequate glycemic control with gemigliptin monotherapy, combination therapy, or mixed regimen of monotherapy and combination therapy was 100, (d) who were lost to follow-up due to unknown causality was 0, (e) who had dropped out due to mild adverse effects was 0, (f) who had dropped out due to moderate adverse effects was 0, (g) who had dropped out due to severe adverse effects was 0, or (h) who had withdrawn voluntarily due to the probability of occurrence of any potential adverse effect was 0. Therefore, the patient compliance was significantly high, on further follow-ups (patient compliance after day 60).

No significant adverse effects were observed among the patients due to the administration of the other hypoglycemic agent, in the combination therapy.

Table 2: Day 30: The occurrence of adverse effects with oral 25 mg gemigliptin monotherapy, combination therapy, or mixed regimen of monotherapy and combination therapy

Adverse effects on day 30	Number of patient occurrence with 25 mg gemigliptin	Z-value	*P*-value
Nasopharyngitis	0	-	Non-significant
Hypoglycemia	0	-	Non-significant
Gastrointestinal disturbances	0	-	Non-significant
Headache	0	-	Non-significant
Nausea	0	-	Non-significant
Rashes	0	-	Non-significant
Urticaria	0	-	Non-significant
Edema	0	-	Non-significant
Weakness	0	-	Non-significant

Table 3: Day 60: The occurrence of adverse effects with oral 50 mg gemigliptin monotherapy, combination therapy, or mixed regimen of monotherapy and combination therapy

Adverse effects on day 60	Number of patient occurrence with 50 mg gemigliptin	Z-value	*P*-value
Nasopharyngitis	0	-	Non-significant
Hypoglycemia	0	-	Non-significant
Gastrointestinal disturbances	0	-	Non-significant
Headache	0	-	Non-significant
Nausea	0	-	Non-significant
Rashes	0	-	Non-significant
Urticaria	0	-	Non-significant
Edema	0	-	Non-significant
Weakness	0	-	Non-significant

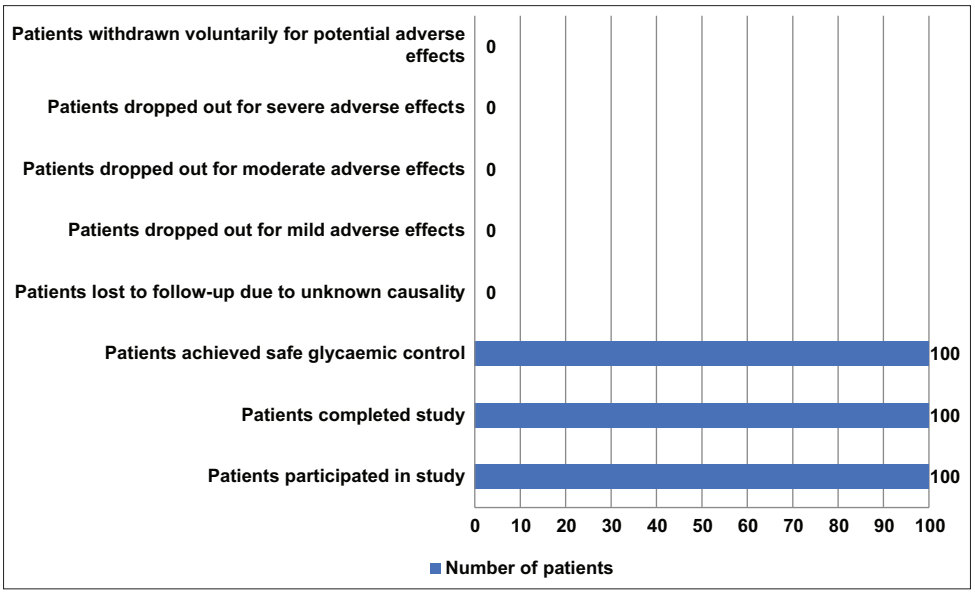

Figure 3: Day 60: Patients' antidiabetic pharmacotherapeutic compliance for gemigliptin therapy

Therefore, this study has shown that the administration of oral 25 mg gemigliptin once daily, for 30 days, and then 50 mg gemigliptin once daily, for the next 30 days, in monotherapy, or in combination therapy, or in a mixed regimen of monotherapy and combination therapy, with another oral hypoglycemic agent, was safe and tolerable, with significantly high patient compliance (i) on day 0, (ii) on day 30 (for any adverse effect between day 0 and day 30), (iii) on day 60 (for any adverse effect between day 30 and day 60), and (iv) on further follow-ups.

DISCUSSION

According to the International Diabetes Federation, almost 415–425 million patients are T2D, including two-thirds adults of 20–64 years.[1,2]

Table 4: Follow-ups: The occurrence of adverse effects with oral 50 mg gemigliptin monotherapy, combination therapy, or mixed regimen of monotherapy and combination therapy

Adverse effects on follow-ups	Number of patient occurrence with 50 mg gemigliptin	Z-value	*P*-value
Nasopharyngitis	0	-	Non-significant
Hypoglycemia	0	-	Non-significant
Gastrointestinal disturbances	0	-	Non-significant
Headache	0	-	Non-significant
Nausea	0	-	Non-significant
Rashes	0	-	Non-significant
Urticaria	0	-	Non-significant
Edema	0	-	Non-significant
Weakness	0	-	Non-significant

The qualitative pharmaco-analysis of gemigliptin elucidated several hypotheses which have specified that DPP-4 inhibitors might accelerate beta-cell regeneration, prevention from pancreas islet hypertrophy and insulin. They might also improve the beta-cell function, which remains unaltered with the food intake, although some studies found no change in the incretin effect. They might even facilitate the adaptability of the beta-cells to insulin resistance, in consequence causing a glucose overload, with a decrease in the overall insulin exposure and the pro-insulin-to-insulin ratio.[2]

The different diabetic complications arise due to the various pathopharmacological mechanisms, such as polyol pathway, hexosamine pathway, inflammatory responses, oxidative pathways, peroxidation, glucotoxicity, and lipotoxicity; oxidative stress playing a crucial role.[3]

In this study, there was the absence of any significant occurrence of adverse effects, on days 0, 30, 60, and further follow-ups, with varying doses of gemigliptin therapy. The analyses of the different patient compliance attributes, on days 0, 30, 60, and further follow-ups, showed that the patient compliance was significantly high, throughout.

Thus, this study amply corroborated not only the efficacious pharmacological functioning of gemigliptin, as a type-II antidiabetic drug, well reflected from its high pharmacotherapeutic compliance but it also possesses a significantly splendid associative correlation between the maximal patient adherence rate and the pharmacovigilance drug safety, with the augmenting drug doses.

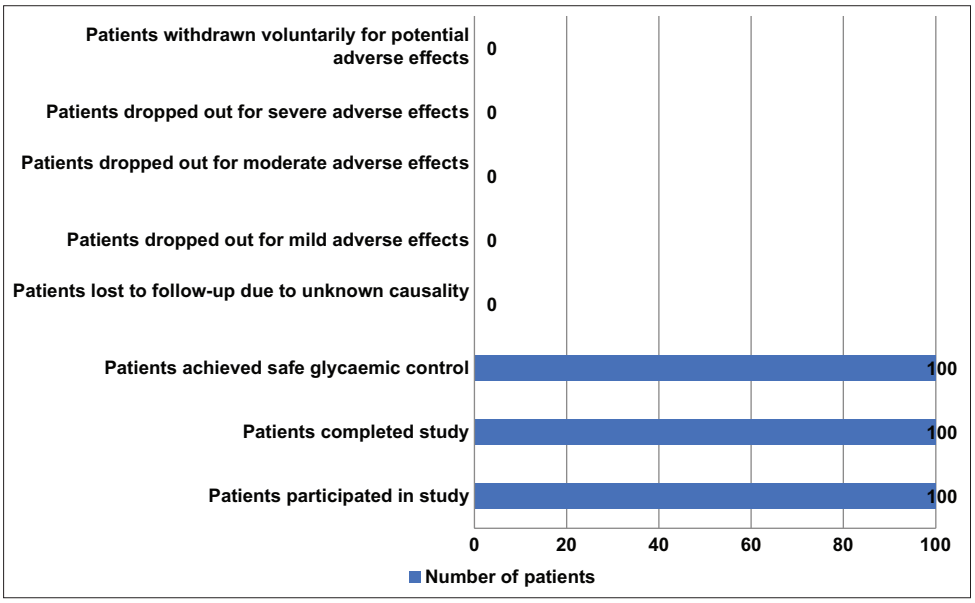

Figure 4: Follow-ups: Patients' antidiabetic pharmacotherapeutic compliance for gemigliptin therapy

CONCLUSIONS

As a conclusion, in this study, there was the absence of any significant occurrence of adverse effects, on days 0, 30, 60, and further follow-ups, with gemigliptin monotherapy, combination therapy, and mixed regimen of monotherapy and combination therapy. The analyses of the different patient compliance attributes, on days 0, 30, 60, and further follow-ups, showed that the patient compliance was significantly high, throughout. Therefore, through this study, it was concluded that gemigliptin was safe and tolerable, at varying drug doses, with significantly high pharmacotherapeutic patient compliance.

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