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Efficacy of Alogliptin as Add on Therapy with Metformin Among Inadequately Control Type 2 Diabetes Mellitus Patients Attending Rajshahi Diabetic Association General Hospital

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Abstract: ***Background:*** Globally, Type 2 diabetes mellitus (DM) is a leading cause of morbidity and mortality and oral antidiabetic medications are an essential part of the treatment plan. While long-term blood glucose management can be challenging by using monotherapy antidiabetic medications, combination therapy with various modes of action is frequently required. ***Methods:*** This quasi-experimental study was conducted in the Department of Pharmacology and Therapeutics, Rajshahi Medical College, Rajshahi in collaboration with Rajshahi Diabetic Association General Hospital (RADAS), Rajshahi on Type 2 DM patients who had inadequate glycemic control with Metformin and diet with lifestyle modification therapy. Based on predefined eligibility criteria, a total number of 42 Type 2 DM patients of both sexes were included in the study. Tablet Alogliptin 25mg as once-daily dose was added after breakfast to the ongoing treatment of tablet Metformin 1000mg for each patient and was followed up at the end of 4, 8 and 12 weeks of drug administration. ***Results:*** Most (92.90%) of the patients had diabetes ≥ 1-year duration. After administration of Alogliptin as add on therapy with Metformin, overall reduction of FBS, PPBS and HbA1c from baseline to 12 weeks of intervention was found statistically highly significant ($p < 0.001$ in each case). ***Conclusions:*** So, Alogliptin with metformin might be used as an 1st line oral antidiabetic drug in case of inadequately control Type 2 diabetes mellitus patients.

Keywords: Type 2 Diabetes Mellitus, Metformin and Alogliptin.

Original Research Article

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Article at a glance:

Study Purpose: *The purpose of this study was to assess the efficacy of Alogliptin as add on therapy with Metformin among inadequately control Type 2 DM patients.*

Key findings: *The present study showed that overall reduction of FBS (9.65 ± 0.29 mmol/L at baseline and 6.54 ± 0.07 mmol/L at 12 weeks) and HbA1c (8.81 ± 0.79% at baseline and to 6.81 ± 0.25% at 12 weeks) from baseline to 12 weeks of Alogliptin treatment were statistically highly significant ($p < 0.001$ in each case).*

Newer findings: *The overall reduction of PPBS from baseline (13.51±1.61 mmol/L) to 12 weeks (7.73±0.38 mmol/L) after intervention was also statistically highly significant ($p < 0.001$).*

Abbreviations: *DM: Diabetes Mellitus, FBS: Fasting blood sugar, HbA1c: Hemoglobin A1c and PPBS: Postprandial blood sugar.*

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INTRODUCTION

Achieving and maintaining glycemic control, treating hypoglycemia and preventing the onset of complications that increase the risk of morbidity and death particularly cardiovascular disease are the key therapeutic objectives for Type

2 diabetes mellitus.[1,2] Alogliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor that is prescribed to individuals with Type 2 diabetes mellitus in order to manage hyperglycemia. When a single dosage of the powerful and highly specific DPP-4 inhibitor Alogliptin is given to individuals with Type 2 diabetes mellitus, the patients' plasma DPP-4 activity is rapidly and sustainably inhibited and their postprandial blood sugar level is significantly decreased.[3] Compared to either medication alone, the combination of Alogliptin and Metformin dramatically improve glycemic control in the obese group. For people with Type 2 diabetes mellitus, Alogliptin is also used in conjunction with diet and exercise to lower blood sugar levels. It regulates blood sugar by boosting the body's production of insulin and GLP-1. Additionally, this medication may lessen the risk of heart attack, stroke and other diabetes-related issues such as kidney failure, nerve damage, changes in or loss of vision in the eyes, gum disease and nerve damage.[4] In healthy patients, peak inhibition of DPP-4 happens two to three hours after a single dosage. At 24 hours, DPP-4 inhibition is maintained above 80% for dosages larger than or equal to 25 mg. Over the course of eight hours after a standardized meal, Alogliptin also reduces postprandial glucagon while raising postprandial active GLP-1 levels in comparison to a placebo.[5] The effectiveness of Alogliptin in the majority of western populations has been well-documented.[6] Even though several studies on Asian populations have been published in Japan, there weren't much statistics on them.[7] To enhance the clinical profile of Alogliptin, further information on Asian patients was needed.[8] In Bangladesh, there wasn't a single published study on the use of Alogliptin to treat Type 2 diabetes. This study's primary goal was to evaluate the effectiveness of Alogliptin as a supplement to Metformin for patients with Type 2 Diabetes Mellitus who were not receiving enough control over their condition. The findings might be helpful for doctors in making precise decisions about adding Alogliptin to Metformin therapy for patients with insufficient glycemic control from Type 2 diabetes mellitus though receiving diet and lifestyle adjustments.

METHODS

This was a quasi-experimental study and conducted in the Department of Pharmacology and Therapeutics, Rajshahi Medical College, Rajshahi in collaboration with Rajshahi Diabetic Association General Hospital (RADAS), Rajshahi for 1 year from July 2022 to June 2023. In this study, study population were Type 2 diabetes mellitus patients who had inadequate glycemic control with Metformin and diet with lifestyle modification therapy and were attending Rajshahi diabetic association general hospital during the study period. Selection of 42 Type 2 diabetes mellitus patients without good glycemic control was done on the basis of inclusion and exclusion criteria and informed written consent was taken from all respondents before participation in this study. Data were collected by face-to-face interview with the help of a semi-structured questionnaire to elicit information of each respondent on sociodemographic profile as well as other variables of interest. Patients were purposively assigned to the once daily Alogliptin 25mg with Metformin 1000mg tablet (administered after breakfast) and medication was continued up to 12 weeks after the intervention. Efficacy was assessed by measurement of FBS, PPBS and HbA1c at baseline and 12 weeks after treatment. After collecting, data were analyzed via Statistical Package for the Social Sciences software, version-24. Qualitative variables were described by frequency distribution while quantitative variables were described by the mean and standard deviation. The efficacy of Alogliptin was assessed by repeated measure ANOVA statistics. A p value < 0.05 was statistically significant for all tests.

RESULT

Table 1: Distribution of patients according to background variables (n = 42)

Variables	
Mean age	50.67 ± 12.33 years
Mean BMI	23.67 ± 2.79 kg/m^2
Gender	
Male	32 (76.19%)

Female	10 (23.81%)
Educational status	
Upto SSC	16 (38.10%)
Upto HSC	12 (28.60%)
Graduate & above	8 (19.00%)
Upto PSC	6 (14.30%)
Duration of diabetes since 1st diagnosis (years)	
Less than 1 year	3 (7.10%)
1 year and above	39 (92.90%)

Mean age and BMI of the respondents were 50.67±12.33 years and 23.67 ± 2.79 kg/m², respectively. Majority (76.19%) were male and 23.81% were female, male to female ratio was roughly 3:1. Educational status of the patients revealed that 38.10% of the patients had upto SSC, 28.60% had upto HSC, 19.00% had graduate & above and 14.30% had upto PSC level of education. Duration of diabetes showed that most (92.90%) of the patients had diabetes 1 year and above duration and 7.10% had less than 1-year duration (Table 1).

Table 2: Monitoring of fasting blood sugar, PPBS and HbA1c at different time interval (At baseline n=42, At 4 weeks n=41, At 8 weeks n=40 and At 12 weeks n=37)

Variables	Time of evaluation				F-value
	At baseline	At 4 weeks	At 8 weeks	At 12 weeks	P-value#
Level of FBS (mmol/L)	9.65 ± 0.29	8.22 ± 0.17	7.23 ± 0.11	6.54 ± 0.07	3258.92 < 0.001
Level of PPBS (mmol/L)	13.51 ± 1.61	10.55 ± 1.05	8.56 ± 0.75	7.73 ± 0.38	6635.11 < 0.001
Level of HbA1C (%)	8.81 ± 0.79	8.12 ± 0.63	7.38 ± 0.44	6.81 ± 0.25	10475.71 < 0.001

(Data were analyzed using Repeated Measure ANOVA statistics and were presented as mean±SD.)

The mean FBS at baseline was 9.65 ± 0.29 mmol/L which decreased to 8.22 ± 0.17 mmol/L at the end of 4 weeks, 7.23 ± 0.11 mmol/L at the end of 8 weeks and then to 6.54 ± 0.07 mmol/L at the end of 12 weeks of administration of Alogliptin as add on therapy with Metformin. So, the overall reduction of FBS from baseline to 12 weeks after intervention was statistically highly significant ($p < 0.001$). The mean PPBS at baseline was 13.51±1.61 mmol/L which decreased to 10.55±1.05 mmol/L at the end of 4 weeks, 8.56±0.75 mmol/L at 8 the end of weeks and then to 7.73±0.38 mmol/L at the end of 12 weeks of administration of Alogliptin as add on therapy with Metformin. So, the overall reduction of PPBS from baseline to 12 weeks after intervention was statistically highly significant ($p < 0.001$). The mean HbA1c at baseline was 8.81 ± 0.79% which significantly reduced to 8.12 ± 0.63% after 4 weeks, 7.38 ± 0.44% after 8 weeks and to 6.81 ± 0.25% after 12 weeks of intervention ($p < 0.001$) (Table 2).

DISCUSSION

Although the origin and etiology of diabetes mellitus can vary greatly, it always involves defects in either insulin secretion or response, or both at some point in the course of the disease. The most prevalent kind of diabetes mellitus, known as type 2 diabetes, is characterized by hyperglycemia, insulin resistance and relative insulin insufficiency. Due to the progressive nature of Type 2 diabetes mellitus, the majority of patients eventually need numerous anti-diabetic medicines to maintain glycemic control. When treating elevated blood sugar levels in Type 2 diabetes mellitus, Metformin and Alogliptin may be taken in conjunction with a healthy diet and exercise regimen. By blocking the breakdown of incretin hormones, Alogliptin prolongs the activity of these hormones which stimulate the pancreas to generate more insulin in response to elevated blood sugar levels.In this study, mean age of the patients was 50.67±12.33 years. But mean age was 58.7 ± 9.8 years in a study done by Yamazaki et al.[9] which was not

similar with our study. Dissimilar findings were also found with the studies done by Rosenstock et al.[10], Iwasaki et al.[11] and Takebayashi et al.[12]

One of the main risk factors for prediabetes and diabetes is advanced age. Consequently, compared to the young and middle-aged, the elderly has a higher prevalence of diabetes and prediabetes and are more prone to experience problems with their cardiovascular, retinal, and renal systems.In our study, out of 42 patients, 76.19% were male and 23.81% were female, male to female ratio was roughly 3:1. Male patients were 62.50% in a study conducted by Yamazaki et al.[9]. The percentage was not similar with our study but male patients were predominant in both of the studies. Contradictory findings were found in a study done by Rosenstock et al.[10] where female was predominant group. Dissimilar findings were also found with the study done by Takebayashi et al.[12]

In the current study, mean BMI was 23.67 ± 2.79 kg/m^2. Similar findings were found in a study done by Takebayashi et al.[12] where mean BMI was 24.4 ± 3.9 kg/m^2. Dissimilar findings were found in a study done by Rosenstock et al.[10] where mean BMI was 32.7 ± 5.5 kg/m^2. But more overweight respondents (27.7 ± 6.0 kg/m^2) were found in a study done by Yamazaki et al.[9].Being overweight (BMI of 25-29.9) or affected by obesity (BMI of 30-39.9) or morbid obesity (BMI of 40 or greater), greatly increases your risk of developing Type 2 diabetes mellitus. Losing weight can reverse Type 2 diabetes mellitus but is rarely achieved or recorded. Type 2 diabetes mellitus is generally perceived as progressive and incurable but for many patients it can be reversed with sustained weight loss of around 15 kg.[13]In this study, duration of diabetes of the patients revealed that most (92.90%) of the patients had diabetes 1 year and above duration and 7.10% had less than 1-year duration. Similar findings were found in a study done by Yamazaki et al.[9] where mean duration was 4.0 ± 4.3 years. Similar findings were also found with the studies done by Rosenstock et al.[10] and Iwasaki et al.[11]

In the study, the mean FBS at baseline was 9.65 ± 0.29 mmol/L which decreased to 8.22 ± 0.17 mmol/L at 4 weeks, 7.23 ± 0.11 mmol/L at 8 weeks and then to 6.54 ± 0.07 mmol/L at 12 weeks after administration of Alogliptin as add on therapy with Metformin. So, the overall reduction of FBS from baseline to 12 weeks after intervention was statistically significant ($p < 0.001$). Similar findings were found in a study done by Yamazaki et al.[9] where FBS at baseline was 176.0 ± 44.2 mg/dl which reduced to 156.7± 35.6 mg/dl at 4 weeks, 155.0 ± 36.8 mg/dl at 8 weeks and 158.8 ± 34.2 mg/dl at 12 weeks of intervention of Alogliptin and Metformin and it was statistically significant ($p < 0.05$). Similar findings were also found with the studies done by Seino et al.[7], Pan et al.[8] and Nauck et al.[14] In our study, the mean PPBS at baseline was 13.51±1.61mmol/L which decreased to 10.55±1.05 mmol/L at 4 weeks, 8.56±0.75 mmol/L at 8 weeks and then to 7.73±0.38 mmol/L at 12 weeks after administration of Alogliptin as add on therapy with Metformin. So, the overall reduction of PPBS from baseline to 12 weeks after intervention was statistically significant ($p < 0.001$). We observed PPBS, but in other studies, it was not observed.

In the current study, the mean HbA1c at baseline was 8.81 ± 0.79% which significantly reduced to 8.12 ± 0.63% after 4 weeks, 7.38 ± 0.44% after 8 weeks and to 6.81 ± 0.25% after 12 weeks of intervention ($p < 0.001$). Yamazaki et al.[9] reported that at baseline HbA1c was 8.17 ± 1.05% and once daily Alogliptin 25 mg plus once-daily Metformin 500 mg reduce HbA1c 7.80 ± 0.88 at 4weeks, 7.52± 0.73% at 8 weeks and 7.42 ± 0.71% at 12 weeks. Yamazaki et al.[9] also showed that once daily Alogliptin 25 mg plus once-daily Metformin 500 mg was superior to once-daily Alogliptin 25 mg plus twice-daily Metformin 250 mg in terms of lowering HbA1c and the reduction was statistically significant ($p < 0.05$). However, the fasting blood sugar levels were significantly lower for once-daily Alogliptin 25 mg plus twice-daily Metformin 250 mg than for once-daily Alogliptin 25 mg plus once-daily Metformin 500 mg. Similar findings were also found with the studies done by Rosenstock et al.[10], Takebayashi et al.[12], Seino et al.[7], Pan et al.[8] and Nauck et al.[14]

A healthy diet, regular physical activity, maintaining a normal body weight and avoiding tobacco use are ways to prevent or delay the onset of Type 2 diabetes mellitus. Diabetes can be treated and its consequences avoided or delayed with diet, physical activity, medication and regular screening and treatment for complications. Anti-diabetic

medications may be monotherapy or combination therapy. Alogliptin is a newer drug and it might be used in control of diabetes as monotherapy or combination therapy.

CONCLUSION

There was statistically highly significant ($p < 0.05$) reduction of FBS, PPBS and HbA1c after adding Alogliptin with Metformin. It could be concluded that Alogliptin along with Metformin might be used effectively in lowering blood sugar levels in patients with Type 2 diabetes mellitus.

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Authors' contributions

MHR, SSS, and MMI: Concept and design, data acquisition, interpretation, drafting and final approval. MHR, PA, SA, MA and TN: Data acquisition, interpretation, drafting, final approval and agree to be accountable for all aspects of the work.

Declarations

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Conflict of interest

Authors declared no conflict of interest.

Ethical approval

Ethical approval of the study was obtained from the Ethical Review Committee, Rajshahi Medical College, Rajshahi. Informed consent was taken from all participants. All the study methodology was carried out following the relevant ethical guidelines and regulations.

Consent for publication: Taken.

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