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Original Research Article

Once daily versus twice daily Linagliptin effect on glycemic levels in type 2 diabetes mellitus- an observational study

Riyaz Mohammed[1]*, Mohammed Azfar Ali[2]

[1]Department of Medicine, M.N.R Medical College, Sangareddy, Telangana, India
[2]Department of Medicine, Esani Diabetes and Multispecialty Centre, Hyderabad, Telangana, India

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***Correspondence:**
Dr. Riyaz Mohammed,
E-mail: riyazesani@hotmail.com

ABSTRACT

Background: DPP-4 is widely distributed in endothelial cells, pancreas, uterus, liver, salivary glands, lymph node, spleen, and thymus. DPP-4 regulates glucagon-like peptide (GLP)-1, and glucose-dependent insulin tropic peptide (GIP) which leads to glucose homeostasis via enhancing insulin secretion and suppression of glucagon, which results in control of post-prandial and fasting hyperglycemia.
Methods: These 40 patients who were enrolled as per the inclusion criteria of receiving metformin dosage of 2 gram per day in established type 2 diabetes mellitus patients with no comorbidities. these patients were divided randomly into two groups comprising of 20 patients each, group A received linagliptin 5 mg per day in addition to metformin 1gm twice daily whereas group B received linagliptin 5 mg per day in a fixed dose (Linagliptin + metformin) of 2.5/1000 twice daily.
Results: In the present observational study, the mean age in group A was 46.7±9.4 compared to 51.65±9.9 in group B, p >0.05, mean BMI in group A was 27.8±1.1 compared to 27.28±0.93 in group B p >0.05, Mean FBS in group A was 157.9±24.1 compared to 146.2±21.8 in group B p >0.05, Mean PPBS in group A was 245.8±32.7 compared to 246.2±39.3 in group B p >0.05 and Mean HbA1c in group A was 7.67±0.58 compared to 7.6±0.5 in group B p >0.05. Group A patients were initiated on once daily linagliptin, there was a significant reduction in FBS, PPBS and HbA1c at the end of 6 months p <0.001. Similarly, Group B patients who were initiated on twice daily linagliptin also showed a significant reduction in FBS, PPBS and HbA1c at the end of 6 months p <0.001.
Conclusions: The addition of linagliptin to metformin treatment was effective and well tolerated in patients with type 2 diabetes. Linagliptin add-on to metformin during the early course of treatment helps in delaying the exhaustion of pancreatic islet function. Plasma concentrations of linagliptin decline in at least a biphasic manner with a long terminal half-life (>100 hours), related to the saturable binding of linagliptin to DPP-4. The prolonged elimination phase does not contribute to the accumulation of the drug. Addition of linagliptin to metformin has shown a significant reduction in FBS, PPBS and HbA1c.

Keywords: DDP-4, Glycemic levels, Glycosylated haemoglobin, Linagliptin, Metformin, Type 2 diabetes mellitus

INTRODUCTION

The DPP-4 family of gene includes the various enzymes such as DPP-4, 8, 9, 6, 10, catalytically inactive proteins and fibroblast activation protein (FAP). DPP-4 is widely distributed in endothelial cells, pancreas, uterus, liver, salivary glands, lymph node, spleen, and thymus. DPP-4 regulates glucagon-like peptide (GLP)-1, and glucose-dependent insulin tropic peptide (GIP) which leads to glucose homeostasis via enhancing insulin secretion and suppression of glucagon, which results in control of post-prandial and fasting hyperglycemia. Other substrates of DPP-4 are neuropeptide-Y (NPY) and substance P. NPY

plays significant role in appetite, control of blood pressure and energy homeostasis, whereas substance P plays a role in pain and inflammation.[1]

DPP4 enzyme causes breakdown of incretin hormones like GLP-1 and GIP. Both the hormones of incretins are involved in the homeostasis of glucose, levels of Incretin hormones are elevated after each meal and during the rest of day it is lower basal level. Linagliptin is a DPP-4 inhibitor which increases the concentrations of active hormones of incretin, which results in stimulation of release of insulin and decreases the glucagon levels.[1,2]

Metformin is widely used as an oral agent for the treatment of type 2 diabetes mellitus. It is recommended as an initial monotherapy. Metformin helps in weight loss and has a record of efficacy and safety, with a lowest risk of hypoglycaemia.[3]

Multiple studies have shown that both monotherapy and Combination therapy of linagliptin with metformin have resulted in significant reduction in glycemic levels.[4] Hence, the current study aims to evaluate the role of combination of linagliptin and metformin as once daily and twice daily formulations on glycemic control.

METHODS

390 Known diabetic patients were selected, out of which only 40 patients were eligible for this observational study as per the criteria.

Inclusion criteria

- Men and women with established type 2 diabetes (19-67 years of age)
- HbA1c: 7.0-9.5%
- Diagnosed type 2 diabetic mellitus and is on metformin only.

Exclusion criteria

- Type 1diabetes mellitus
- Pre-existing cardiac disease
- Pre-existing renal impairment (serum creatinine≥1.4 mg/dl for males or ≥1.2mg/dl in females)
- Elevated levels of hepatic enzymes
- Creatine phosphokinase (greater than two times the upper limit of normal)
- Patients on pre-existing other OHA like Sulphonylurea, Insulin
- SGLT 2 inhibitors, and alpha glucosidase inhibitors.

These 40 patients who were enrolled as per the inclusion criteria of receiving metformin dosage of 2 gram per day in established type 2 diabetes mellitus patients with no comorbidities. these patients were divided randomly into two groups comprising of 20 patients each, group A received linagliptin 5 mg per day in addition to metformin 1gm twice daily whereas group B received linagliptin 5 mg per day in a fixed dose (linagliptin + metformin) of 2.5/1000 twice daily. The patients were followed up for a period of 6 months and efficacy of once daily linagliptin was compared to twice daily linagliptin using SPSS statistical software and appropriate statistical tests.

RESULTS

In the present study the demographics in group A was compared with group B (Table 1) prior to initiation of linagliptin it was observed that there was no statistical significance observed between either groups, the mean age in group A was 46.7±9.4 compared to 51.65±9.9 in group B, p >0.05, mean BMI in group A was 27.8±1.1 compared to 27.28±0.93 in group B p >0.05, Mean FBS in group A was 157.9±24.1 compared to 146.221.8 in group B p >0.05, Mean PPBS in group A was 245.8 ±32.7 compared to 246.2±39.3 in group B p >0.05 and Mean HbA1c in group A was 7.67±0.58 compared to 7.6±0.5 in group B p >0.05.

Table 1: Pre-study demographics.

Parameter	Group A	Group B	p value
Age	46.7±9.4	51.65±9.9	0.117
Sex (m/f)	16/4	13/7	0.288
BMI	27.8±1.1	27.28±0.93	0.071
FBS	157.9±24.1	146.2±21.8	0.116
PPBS	245.8±32.7	246.2±39.3	0.97
HbA1c	7.67±0.58	7.6±0.5	0.685

Group A (n=20) patients were initiated on once daily linagliptin, there was a significant reduction in FBS, PPBS and HbA1c at the end of 6 months p <0.001. Similarly, Group B patients who were initiated on twice daily linagliptin also showed a significant reduction in FBS, PPBS and HbA1c at the end of 6 months p <0.001 (Table 2).

Table 2: Paired t test comparison before and after addition of linagliptin.

Parameter	Pre-study	Post study	p value
Group A			
FBS	157.9±24.1	130.75±23	<0.001
PPBS	245.8±32.7	205.7±34.9	<0.001
HbA1c	7.67±0.58	7.14±0.32	<0.001
Group B			
FBS	146.2±21.8	121.25±19.5	<0.001
PPBS	246.2±39.3	199±41.7	<0.001
HbA1c	7.6±0.5	7.11±0.37	<0.001

At the end of 6 months the glycemic control observed with once daily linagliptin 5mg/day versus twice daily (2.5mg twice a day) linagliptin was compared using independent t test, there was no significant difference observed in the glycemic control observed with once

daily linagliptin and twice daily linagliptin p >0.05. There was no significant difference in the amount of reduction attained with respect to FBS, PPBS and HbA1c with once daily or twice daily linagliptin.

Table 3: Comparison of linagliptin once daily versus twice daily.

Parameter	Group A	Group B	p value
FBS	130.75±23	121.25±19.5	0.167
PPBS	205.7±34.9	199±41.7	0.585
HbA1c	7.14±0.32	7.11±0.37	0.821

DISCUSSION

Patients diagnosed with T2DM find it difficult to achieve and maintain normoglycemia using monotherapy of metformin alone. A combination therapy of drugs can play an important role in management of disease and attaining normoglycemia. Addition of the DPP4 inhibitor linagliptin has been shown to improve glycemic control for patients who are not well controlled with metformin. Combination of linagliptin and metformin helps in attaining better glycemic control via synergistic and complementary mechanisms. In the present study addition of linagliptin has resulted in clinically and statistically significant reductions in FBS, PPBS and HbA1C, lowering effect achieved with once daily linagliptin was comparable with twice daily linagliptin.

Haak T et al, lasted for 24-weeks trial had selected two groups, one group received linagliptin 2.5 mg twice daily + either low (500 mg) or high (1000 mg) dose metformin twice a day. The mean HbA1c change was from baseline-1.7% for the group of high-dose metformin + linagliptin, 1.3% for low-dose metformin + linagliptin.[4] Chen Y et al, in this study 300 Asian type 2 diabetes mellitus were randomized to linagliptin or placebo at a 2:1 ratio. After 24 weeks of treatment it was shown that there was significant reduction of HbA1c.[5]

Multiple trails have shown that patients on linagliptin have achieved good reductions in HbA1c with a very low incidence of hypoglycemia and it didn't have any impact on weight i.e. weight neutral. Various other gliptins like Saxagliptin and Alogliptin had cardiovascular safety issues. SAVOR-TIMI 53 (Saxagliptin assessment of vascular outcomes recorded in patients with diabetes mellitus- thrombolysis in myocardial infarction 53) and examine trails (examination of cardiovascular outcomes with Alogliptin versus standard of care), concerns were raised regarding CHF due to the finding of a these two studies showed significantly increased risk of hospitalization due to CHF which was associated with Saxagliptin therapy, and there was non-significant hazard ratio for Alogliptin of above 1.0 in EXAMINE trails, but these concerns were not there with Linagliptin.[6,7] A clear answer on the safety profile of CV in relation to linagliptin will be provided by the cardiovascular outcome study of linagliptin versus glimepiride in patients with type 2 diabetes (CAROLINA), the results are expected to report between 2017 and 2018.[8]

Linagliptin can be used without dose adjustment in patients with reduced renal function. Among Asian populations, metformin is used under dosage due to risk of gastrointestinal issues. Inagaki N et al, study was carried out in Japanese patients for comparison of once daily linagliptin with metformin (once to three times daily) as an add-on therapy to sulfonylurea or an a-glucosidase inhibitor, it has shown significant reduction of HbA1c and adverse events like hypoglycemia were similar in all the groups.[9]

In Asian population of type 2 diabetes mellitus there is significant post prandial spikes in glycemic levels which is better addressed in patient on DPP-4 especially linagliptin. In specifically, Asian diet is a carbohydrate-rich diet which causes elevation of post-prandial glucose (PPG) and glycemic variability and these DPP-4 inhibitors primarily affect control of PPG excursions. Zeng et al, study has shown there is a statistically significant reduction in 2-h PPG with linagliptin in an Asian population.[10]

CONCLUSION

Initial combination therapy of DPP4 inhibitor and metformin in treatment of T2DM is advantageous as it targets the numerous pathophysiologic defects early. Current study as the lowering effect achieved with twice daily linagliptin was comparable with once daily linagliptin, A simplified dosage regimen, which is an advantage over separately administered medications that increase the pill burden, facilitates improved adherence and better glycemic control on a long-term basis.

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