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COMPARISON OF EFFICACY AND SAFETY OF TENELIGLIPTIN VERSUS SITAGLIPTIN AS ADD ON TO METFORMIN IN TYPE 2 DIABETES MELLITUS AT JLNMC, BHAGALPUR, BIHAR

Pharmacology

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ABSTRACT

Introduction: Diabetes mellitus (DM) is a leading cause of mortality and an increasing health burden with a prevalence of 8.3% globally and 9.1% in India (IDF). Prevention of complications and improving quality of life are the principle goals in its management. DPP-4 inhibitors have a potential vasoprotective effect mediated by stromal cell derived factor-1a. Teneligliptin a novel, highly selective, more potent agent compared to Sitagliptin provides sustained glycaemic control, decreases cardiovascular complications, has additional beneficial pleiotropic metabolic effects and also safe in renal impairment.

Objective: To evaluate the glycaemic and non-glycaemic effects of Teneligliptin vs Sitagliptin as add on therapy to metformin.

Materials and methods: 60 subjects with T2DM who failed to achieve glycaemic control with metformin (500mg TID) alone for 3 months were randomized in 1:1 ratio to receive Teneligliptin 20mg OD and Sitagliptin 100mg OD as add on therapy. Patients were followed up at 4, 8 and 12 weeks for glycaemic and non-glycaemic effects. Adverse drug reactions (ADRs), if any were recorded and graded according to severity.

Results: There was a statistically significant decrease in FBS ($p<0.05, p<0.001$) and PPBS ($p<0.01, p<0.001$) in patients treated with Teneligliptin on week 8 & week 12 from baseline compared to those treated with Sitagliptin. The reduction in HbA_{1c} ($p<0.0001$), LDL-CH ($p<0.0001$) & TC ($p<0.001$) on week 12 from baseline was also significantly more in the Teneligliptin group.

Conclusion: Teneligliptin may be an effective and safe treatment option in reducing both glycaemic and non-glycaemic parameters as an add-on therapy in Type 2 DM with good patient tolerability.

KEYWORDS

Teneligliptin, Type 2 DM, Sitagliptin, DPP4 Inhibitors.

INTRODUCTION

Diabetes mellitus (DM) a major lifestyle disease is undoubtedly the most challenging public health problem of 21st centuryand one of the leading causes of morbidity and mortality worldwide and a major problem in India. The number of patients with type 2 DM is rapidly increasing worldwide, especially in the Asian countries, because of aging population and changes in dietary habits. According to the Diabetes Atlas 2006 by the International Diabetes Federation, the number of people with diabetes in India currently around 40.9 million is expected to rise to 69.9 million by 2025 unless urgent preventive steps are taken.

Diabetes is managed using a stepwise approach involving lifestyle modifications, followed by addition of oral antidiabetes drugs such as metformin if HbA_{1C} level remains above 7.0%. Despite initial monotherapy, majority of patients fail to achieve glycemic goals and may require combination therapy. Dipeptidyl peptidase (DPP)-4 inhibitors are a relatively new class of oral anti-hyperglycaemic drugs that have shown to improve beta cell function and/or neogenesis. Due to the complementary mechanisms of action, a combination of metformin (decreases insulin resistance) with a DPP 4 inhibitor (improves beta cell function) helps in maintaining HbA_{1C} within the target range.

DPP 4 inhibitors are considered to be more effective in Asian patients because diabetes is due to insufficient insulin production when compared to the Caucasians who usually have insulin resistance. Previous studies have shown a reduction in HbA_{1C} by 0.6% by sitagliptin 100 mg/ day and 0.7% by teneligliptin 20 mg/day. Meta-analysis indicated DPP 4 inhibitors to have a beneficial effect on cholesterol that could contribute to reduction of cardiovascular risk. Comparative inhibition studies showed teneligliptin exhibited more potent inhibition of DPP 4 enzyme than sitagliptin because of its unique J- shaped structure and anchor lock domain.

Few studies have examined differences in control of glycaemic and non glycaemic parameters between different DPP4 inhibitors. In view of the limited body of studies between teneligliptin and sitagliptin, we conducted a randomized prospective comparative study using HbA_{1C} as the primary tool to investigate the blood glucose level.

MATERIALS AND METHODS

This was a randomized, open-label, comparative study conducted at Department of Pharmacology, JLNMC, Bhagalpur, Bihar among 60 patients who attended the out-patient Department of Medicine in Jawaharlal Nehru Medical College and Hospital, Bhagalpur, Bihar. Thepatients who failed to respond to metformin 500 mg tid with adequate diet and exercise were randomized into 2 groups in a 1:1 ratio of 30 patients in each group and randomization done using the computer generated randomization sequence. Group 1 received teneligliptin 20 mg once daily, and group 2 received sitagliptin 100mg once daily. Concomitant medications like anti-hypertensives and lipid-lowering drugs were left unchanged during the study period. Patients of both groups were instructed to strictly maintain dietary habits and daily activities during the course of the study. They were assessed at the outpatient visit four times: at baseline, 4, 8 and 12 weeks. At baseline, blood samples for bio-chemical measurements were assessed and also repeated at follow up visits. Adverse drug reactions events if any were recorded in CDSCO-IPC form.

Selection criteria

Patients willing to give written informed consent of either sex, aged between 18 to 80 years, diagnosed with Type 2 DM according to ADA criteria, who did not achieve glycaemic target with metformin alone for 6 months and having HBA_{1C} levels between 7-9% on monotherapy with metformin 1.5g/day for 6 months prior to visit were included in the study. Patients who suffered an attack of acute coronary syndrome, transient ischaemic attack or stroke in the past three months, those with hepatic disease (serum level of ALT, AST, Alkaline phosphatase >3times the upper limit of normal), type 1 diabetes mellitus, severe ketosis, coma or reduced level of consciousness within the past 6 months due to diabetes, severe infection, pre or post operative, severe

trauma, history of a chronic intestinal disease associated with absorption and digestive problems, moderate or severe renal dysfunction (creatinine clearance <50ml/min, serum creatine level >1.5mg/dl in men and 1.3mg/dl in females) or those with history of type 1 DM or secondary form of diabetes due to pancreatic diseases were excluded from the study.

STATISTICALANALYSIS

All categorical variables were represented in terms of percentage, continuous variables were represented in terms of mean ± standard deviation and inter and intra group comparisons was done using unpaired t-test and ANOVA respectively. The level of significance was set at $p<0.05$. Statistical analysis of data was performed using Vassar stats.

RESULTS

A total of 60 patients were included in the study. There was no statistical differences between both the groups at baseline with respect to demographic characteristics, glycaemic and non-glycaemic parameters. (Table 1).

The change in HbA_{1C} from baseline was the most important primary end point of our study. At the end of 12 weeks of treatment, both groups had a decline in HbA_{1C} but the teneligliptin group had the greatest (0.9 ± 0.11 % vs 0.6 ± 0.14, p= <0.0001). The baseline FBS and PPBS values in both the groups were matched. There was a statistically significant decrease in FBS at end of week 8 ($p<0.05$) and week 12 ($p<0.001$) from baseline in patients treated with Teneligliptin compared to those treated with Sitagliptin. The reduction in PPBS was also statistically significant at week 8 ($p<0.01$), and week 12 ($p<0.001$) in Teneligliptin group when compared to those treated with Sitagliptin.The total cholesterol (TC) and Low density lipoproteins (TC, LDL) were the non-glycaemic parameters assessed and followed up at week 12. Baseline values for non glycaemic parameters in both the arms were matched as tabulated in Table 1. At the end of 12 weeks though both the groups showed a downtrend, the decrease was higher in the teneligliptin group at the end of 12 weeks (TC: $p<0.001$, LDL: $p<0.0001$).

The most common ADRs experienced in both groups were nausea, constipation and abdominal cramps, few patients also complained of joint pain and hypoglycemia. Across both the groups, no severe ADRs were recorded. Gastro-intestinal effects (nausea, constipation, abdominal cramps) were 15% in both groups, higher incidence of joint pain (10% Vs 5%) were seen in the teneligliptin arm and hypoglycaemia was seen only in the sitagliptin group.

Table 1 : Baseline characteristics of patients

Characteristics	Teneligliptin	Sitagliptin	p-value
Age in years (Mean±SD)	49.5±15.5	47.5±15.5	0.26
Gender • Male • Female	51% 49%	54% 46%	0.37
BMI (Mean±SD)	27.9±4.8	27.3±4.4	0.28
HBA_{1c}(Mean±SD)	8.8±0.35	8.4±0.42	0.18
FBS (Mean±SD)	170±5.5	168±5.5	0.39
PPBS (Mean±SD)	261±4.6	255±4.7	0.33
TC (Mean±SD)	226.4±32.25	229.9±30.1	0.24
LDL (Mean±SD)	165±30.17	154±27.11	0.05

Table 2 : Mean reduction in glycemic and non-glycemic parameters in teneligliptin group

	Baseline	4 weeks	8 weeks	12 weeks	p-value
FBS	170±5.3	148.1±3.2	138.5±2.1	$130.1±1.9^{×}$	0.001
PPBS	261.85±4.5	213.7±3.9	190±2.6	20.1±1.3**	0.03
AbA_{1c}	8.8±0.35	-	-	$7.98±0.65^{\#}$	0.002
TC	226.4±32.25	-	-	$186.2±22.2^{\$}$	0.001
LDL	165±30.1	-	-	$130.7±19.1^{\$\$}$	0.03

Table 3 : Mean reduction in glycemic and non-glycemic parameters in sitagliptin group

	Baseline	4 weeks	8 weeks	12 weeks	p-value
FBS	168±5.5	149±1.4	145±2.2	145±1.7	0.003
PPBS	255±4.7	214.4±2.3	214.5±3.2	206.4±1.6	0.02
AbA_{1c}	8.4±0.42	-	-	7.8±0.55	0.001
TC	299±30.1	-	-	217.4±24.6	0.002
LDL	154±27.11	-	-	152±19.8	0.04

FBS× p- <0.001, PPBS**p-<0.001, HbA_{1C}# p- <0.0001, $TC^{\$}$ p-<0.001, $LDL^{\$\$}$ p-<0.0001

Table 4 : Mean glycaemic parameters between 2 groups

	Teneligliptin	Sitagliptin	p-value
FBS	170±5.3	168±5.5	0.39
• Baseline	148.1±3.2	149±1.4	0.40
• 4 weeks	138.5±2.1	145±1.2	<0.05
• 8 weeks	130.1±1.9	145±1.7	<0.001
• 12 weeks			
PPBS	261.85±4.5	255±4.7	0.33
• Baseline	213.7±3.9	214.4±2.3	0.34
• 4 weeks	190±2.6	214.5 3.2	<0.01
• 8 weeks	204±1.3	206.4±1.6	<0.001
• 12 weeks			
HbA_{1c}	8.8±0.35	8.4±0.42	0.18
• Baseline	7.98±0.65	7.8±0.55	<0.0001
• 12 weeks			

Table 5 : Mean non-glycaemic parameters between 2 groups

	Teneligliptin	Sitagliptin	p-value
TC	226.4±32.25	229±30.1	0.24
• Baseline	186.2±22.2	217.4±24.6	<0.001
• 12 weeks			
LDL	165±30.1	154±27.1	0.05
• Baseline	130.7±19.1	152±19.8	<0.0001
• 12 weeks			

Table 6 : Adverse effects

Adverse Effects	Teneligliptin (n=30)	Sitagliptin (n=30)
Gastro-intestinal side effects	15%	15%
Joint Pain	10%	5%
Hypoglycaemia	None	5%

The most common ADRs experienced in both groups were nausea, constipation and abdominal cramps, few patients also complained of joint pain and hypoglycemia. Across both the groups, no severe ADRs were recorded. Gastro-intestinal effects (nausea, constipation, abdominal cramps) were 15% in both groups, higher incidence of joint pain (10% Vs 5%) were seen in the teneligliptin arm and hypoglycaemia was seen only in the sitagliptin group.

DISCUSSION

In our study, both the groups achieved better glycaemic and non-glycaemic control when compared to the baseline, though teneligliptin group showed a superior decline. Our primary study end point was to assess the change in HbA_{1C}. At week 12, both the groups achieved significant reduction in HbA_{1C} with a greater decline in the Teneligliptin group (0.9 ± 0.11 % vs 0.6 ± 0.14, p= <0.0001). Dual therapy of Teneligliptin with metformin led to a significant HbA_{1C} reduction of 1.07% in studies conducted by Ghosh et al. In a randomized, double-blind, placebo-controlled, parallel-group study by Kadowaki et al, patients (n=324) were randomized to receive teneligliptin 10, 20 or 40 mg, or placebo, once daily before breakfast for 12 weeks. There was a 0.9% reduction in HbA1c with 20 mg teneligliptin which is similar to findings in present study. Similar results were also obtained in a multicentre, randomized, phase III study in Korea. Teneligliptin significantly reduced the HbA1c level (0.94%) from baseline compared with placebo after 24 weeks.

The percentage reduction in HbA1c in sitagliptin group was 0.6%. In a study conducted by Raz et al comparing sitagliptin with placebo, a significant reduction in HbA_{1C} from the baseline at the end of 12 weeks (0.60%) was seen, consistent with the above results. In another study conducted by EuJeong et al, the efficacy of initial combination of sitagliptin with metformin in patients with a history of T2DM was assessed for a study time of 4 years. At the end of 4 years, HbA_{1C} levels significantly reduced (p<0.001). Our study results were similar to above mentioned studies.

Both the groups showed statistically significant effect on glycemic control. The reduction in FBS values at week 8 and 12 was statistically significant in Teneligliptin group in comparison to sitagliptin group. Kutoh et al in a 3 month study of 31 drugnaive Japanese T2DM patients, evaluated teneligliptin daily 20 mg as a monotherapy. This study found a significant reduction in fasting blood glucose (p<0.0002) at the end of 4 weeks from the baseline. Similarly the teneligliptin

group saw a significantly greater decline in PPBS at weeks 8 (HbA_{1C}: $p<0.01$) and 12 ($p<0.001$). But the maximum change in PPBS was observed at week 8 ($p<0.01$). In a Japanese study (n=99), teneligliptin 20 mg significantly reduced 2 h PPBS levels ($p<0.01$) against placebo at breakfast, lunch, and dinner at the end of 4 weeks. The present study showed decrease in PPBS at 8 and 12 weeks.

Reports on the effects of DPP-4 inhibitors in improving insulin resistance and the serum lipid profile in humans are few. A meta-analysis suggested a possible beneficial effect of DPP-4 inhibitors on cholesterol which, although small, could contribute to the reduction of cardiovascular risk. Kusunoki et al showed beneficial effect of Teneligliptin on lipid profile. 14-weeks treatment with Teneligliptin 20mg/day showed significant improvement in lipid profiles. It has been demonstrated that DPP4stimulates lipid accumulation and PPAR-γ expression through cleavage of neuropeptide Y suggesting that DPP4 might stimulate adipocyte differentiation. On the contrary, recent published study showed that DPP4 expression was strongly upregulated during adipocyte differentiation in vitro. Hence, it has been concluded that DPP4 might be a major component in adipose tissue remodeling and cell plasticity. In a meta-analysis, the treatment with DPP4 inhibitors determined a significant reduction of total cholesterol at the end of 24 weeks.

In our study, reduction in TC and LDL which was higher in the teneligliptin arm probably is because of its more sustained inhibition of D2 enzyme. The probable significant effect on non glycemic parameters require further evidence and longer duration of study to assess the significance of DPP 4 inhibitors on non glycemic parameters.

Assessment of ADRs was another important outcome of the study. Based on previous literature, the possible adverse effects encountered by gliptins are GI side effects, joint pain, infections and hypoglycaemia (rare). Gastro-intestinal side effects like abdominal pain and constipation are believed to be due to enhanced activity of incretins. The adverse effects noted in our study were gastrointestinal side effects and joint pain. A single episode of mild hypoglycaemia was also noted in the sitagliptin group.The incidence of adverse events (AEs) was not significantly different between teneligliptin and sitagliptin group in the present study.

After extensive literature search, to the best of our knowledge, the present study is the first to compare efficacy and safety of teneligliptin and sitagliptin as add on to metformin amongst Indian subjects. Randomisation of the study subjects and assessment of the effect on glycaemic and non glycaemic parameters added strength to the study.

The present study had certain limitations. The study was performed in a relatively small number of patients, open label study, LFT and long term effects of DPP4 inhibitors were not evaluated. Glycaemic variability (GV) measured using Continuous Glucose monitoring was not done adding to the limitation of the study.

During post-approval use of Teneligliptin therapy, adverse effects like hepatic dysfunction-associated cases were noted. Post-marketing reports of sitagliptin reported serious allergic reactions, including anaphylaxis, angioedema, and Stevens–

Johnson syndrome. Additionally, close pharmacovigilance monitoring plans are necessary to address the uncertainty regarding AEs of DPP-4 inhibitors, while their potential impact on cardiovascular outcomes would be clarified in the near future after the completion of more relevant long-term studies.

CONCLUSION

It can be concluded that Teneligliptin, a potent DPP4 inhibitor with a long half-life and sustained DPP4 inhibition in comparison to sitagliptin has shown to decrease the fluctuations in glucose levels and suppress the post-prandial hyperglycaemia in type 2 DM patients. Teneligliptin 20mg OD significantly lowered the glycaemic and non-glycaemic parameters in comparison to sitagliptin 100mg OD. Teneligliptin serves as an appropriate add-on to Metformin early in therapy to delay exhaustion of pancreatic islet cell function and may be an effective and safe treatment option in type 2 DM with good patient tolerability.

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