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Research Article

Efficacy and Safety of Fixed-dose Combination of Teneligliptin and Pioglitazone versus Respective Monotherapies in Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Metformin: A Phase III Randomized Parallel Group Study

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Abstract

Background and aims: Teneligliptin, a third generation DPP-4 inhibitor, decreases the degradation of incretins, while Pioglitazone, a potent insulin sensitizer, reduces the glucose output from liver. A combination of these two could be beneficial clinically; and hence a comparative study was planned. **Methods:** A prospective, randomized, double blind, comparative, parallel group multicentre study was planned to evaluate the safety and efficacy of FDC of Teneligliptin 20mg + Pioglitazone 15 mg tablets and FDC of Teneligliptin 20mg + Pioglitazone 30mg tablets versus Teneligliptin 20mg and Pioglitazone 30mg alone in patients with type 2 diabetes mellitus (T2DM), inadequately controlled on Metformin. Eight-six patients were recruited in each arm from fifteen centres across India. The primary endpoint was the change in HbA1c from baseline to week 24. Safety was assessed in terms of hypoglycaemic episodes. **Results:** Patients were matched on demographic and anthropometric parameters. Primary endpoint HbA1c showed significantly more change in FDC groups as compared to monotherapies from baseline to week 12, as well as week 24 ($p < 0.0001$). On similar lines, FBG and PPBG showed significantly more change in FDC as compared to monotherapies ($p < 0.0001$). Moreover, the proportion of patients achieving HbA1c < 7% by week 24 was higher in FDC groups as compared to monotherapy groups. Hypoglycaemic episodes were observed in 3.48% cases on dual therapy, while 1.74% on pioglitazone monotherapy and all were of mild severity and resolved by the end of study. **Conclusion:** The FDC of teneligliptin and pioglitazone has superior and significant control on glycaemic parameters as compared to respective monotherapies and the combination was well tolerated.

Keywords: Fixed-dose combination; Dual therapy; Monotherapy; Glycaemic parameters; Hypoglycaemia

Introduction

Diabetes mellitus is a state of hyperglycaemia due to reduced insulin secretion from pancreatic β cells and increased insulin resistance. Diabetes has become a worldwide epidemic; and according to International Diabetic Federation (IDF) report of 2021, approximately 537 million adults (20-80 years) are living with diabetes. This number is expected to rise to 643 million by 2030 and 783 million by 2045 [1]. On global front, China, India, United States and Russian Federation are the major contributors to overall diabetes prevalence [2]. India is facing challenge with the growing diabetic population, with an estimate of 8.7% patients in the age range of 20 – 70 years, and almost 87 million people in India are predicted to have diabetes by 2030 [3]. Insulin resistance (IR), greater abdominal adiposity and high C-reactive protein (CRP) levels are typically observed among Indian population [4]. In north India, the prevalence of IR, as measured by Homeostasis Model Assessment ($HOMA_{IR}$), in first-degree relatives and controls were 37.8% and 12.47% [5]. In another study from south India, the overall prevalence of IR using HOMA model was 11.2% [6].

Diabetes is a chronic disease and requires lifelong medical attention and treatment to prevent short and long-term complications [7]. Despite the availability of number of oral anti hyperglycaemic agents, maintaining a good glycaemic control in patients is often a challenge [8,9]. Anti-diabetic action of dipeptidyl peptidase-4 inhibitors (DPP4i) are based on two incretin hormones, glucose-like peptide-1 (GLP-1) and Glucose-Dependent Insulinotropic Peptides (GIP). Both are secreted from enteroendocrine cells after meals. The function of incretins is to regulate insulin secretion from pancreatic β cells [10]. In type-2 diabetes, GIP does not modulate glucose-dependent insulin secretion, and hence GIP incompetence is detrimental to β-cell function [11]. GLP-1 plays an important role in the regulation of blood glucose level by stimulating postprandial insulin secretion and inhibits postprandial glucagon secretion, thus controlling the blood glucose levels [12]. DPP-4 inhibitors increase the active levels of GLP-1 hormones and thus improves β-cell function, attaining glycaemic control in type 2 diabetic patients [13]. Teneligliptin is a competitive reversible third generation DPP-4 inhibitor that decreases the degradation of incretins, especially GLP-1, thereby stimulating insulin secretion and suppressing glucagon secretion in a glucose-dependent manner [14]. Teneligliptin has a J-shaped structure with five rings, and four of these directly connect to DPP-4 enzyme, giving enhanced potency and selectivity of drug [15]. Thiazolidinediones (TZDs) are approved for clinical use in T2DM since 1990 [16]. TZDs are peroxisome proliferator-activated receptor-γ agonist. Pioglitazone, a TZD, is the most potent insulin sensitizer that increases insulin sensitivity in muscle, liver and adipose tissue, thereby reducing the glucose output from liver [17,18]. Pioglitazone reduces gluconeogenesis and enhances peripheral glucose utilization and restrains lipolysis [19]. The insulin sensitivity gets improved by diverting the lipids from ectopic sites like skeletal muscle and visceral fat, into subcutaneous adipose tissues [20]. In patients with inadequate glycaemic control by conventional monotherapy, the combination of teneligliptin and pioglitazone is expected to be clinically beneficial. Thus, this clinical study was designed to assess the efficacy and safety of a fixed-dose combination (FDC) of teneligliptin and pioglitazone compared to the respective monotherapies.

Materials and Methods

Study design

This was a phase III, prospective, randomized, double-blind, comparative, parallel-group, multicentre clinical study to evaluate the efficacy, safety and tolerability of FDC of Teneligliptin 20 mg + Pioglitazone 15mg tablets and FDC of Teneligliptin 20 mg + Pioglitazone 30 mg tablets versus Teneligliptin tablets 20mg and Pioglitazone tablets 30 mg in patients with type 2 diabetes mellitus, inadequately controlled on Metformin monotherapy.

The study was conducted at fifteen centres across India and complete recruitment was done in all the centres. Institutional Ethics Committees (IEC) of each study site approved the study protocol accepted by CDSCO/DCGI, including the final version of Informed Consent Form (ICF).

Study endpoints

The primary efficacy endpoint was the mean change in HbA1c from baseline to end of study visit i.e. 24 weeks in each treatment arm. The secondary endpoints were: a) mean change in Fasting Blood Glucose (FBG) and post-Prandial Blood Glucose (PPBG) from baseline to 24 weeks in each arm, b) proportion of patients achieving a therapeutic glycaemic response i.e. HbA1c < 7% at the end of study. The safety endpoints were: hypoglycaemic episodes during the study period, adverse and serious adverse events during the study, and changes in the clinical and laboratory parameters from baseline to end of study.

Sample size

The sample size estimation was planned to establish the superiority of FDC over monotherapy. An effect size of 0.5 for change in HbA1c levels from baseline to week 24 between test and comparator was considered, resulting into a sample of 328 patients that can determine the effect with 95% confidence and 90% power. A standard deviation of 1.1 was considered based on past literature to determine the size. Considering 15% loss to follow-up, a final sample of 385 patients was considered.

Patients

The study population consisted of male and female diabetic patients in the age range of 18 – 65 years, who were on metformin (≥1000 mg/day) for at least 3-months before screening and had inadequate glycaemic control with HbA_1c in the range of ≥7% to ≤10%. After receiving the consent from each patient, demographic details and medical history were taken during the screening visit. Patients were screened for FBG, PPBG, HbA_1c, haematological and biochemical tests, lipid profile, urine examination, and 12-lead ECG. The vital and physical examinations were done at screening and subsequent visits. The excluded patients were those with type 1 DM, history of metabolic acidosis, fasting glucose > 220 mg/dl, BMI > 45 kg/m^2, clinically impaired hepatic and renal functions, significant cardiovascular history, ongoing treatment of arrhythmias, history of anaemia, acute pancreatitis, malignancy, pregnant or breast-feeding females, history of substance abuse.

Randomization

Upon fulfilment of the inclusion / exclusion criteria, patients were randomized to one of the four treatment arms: A) FDC of Teneligliptin 20 mg + Pioglitazone 15 mg tablets (test drug 1), B) FDC of Teneligliptin 20 mg + Pioglitazone 30 mg tablets (test drug 2), C) Teneligliptin 20 mg alone (reference drug 1) and D) Pioglitazone 30 mg alone (reference drug 2). Metformin was administered along with both test and reference products. Randomization to treatment groups was done in 1:1:1:1 proportion, following a block randomization process. The computer-generated randomization codes were referred to include eligible patients in one of these arms. The randomization was concealed from patients, investigators, and study personnel, as the study was double-blinded. The medication required for the entire treatment duration was packed and labelled under Good Medical Practice (GMP) conditions. The randomization team carried out the drug coding and accordingly they were assigned to the individual patient.

Intervention

Patients from each arm were administered the drug as per schedule and instructions provided to ensure compliance with the protocol. The study period spanned over 24 weeks with seven scheduled visits. Patients were instructed to take one tablet orally, to be swallowed as a whole with water in the morning after breakfast around the same time every day, for 168 days (24 weeks). Each patient was provided with a glucometer to record self-monitored glucose levels, at least once a week, and during hypoglycaemic symptoms if any. The final analysis sample per group is given in Figure 1.

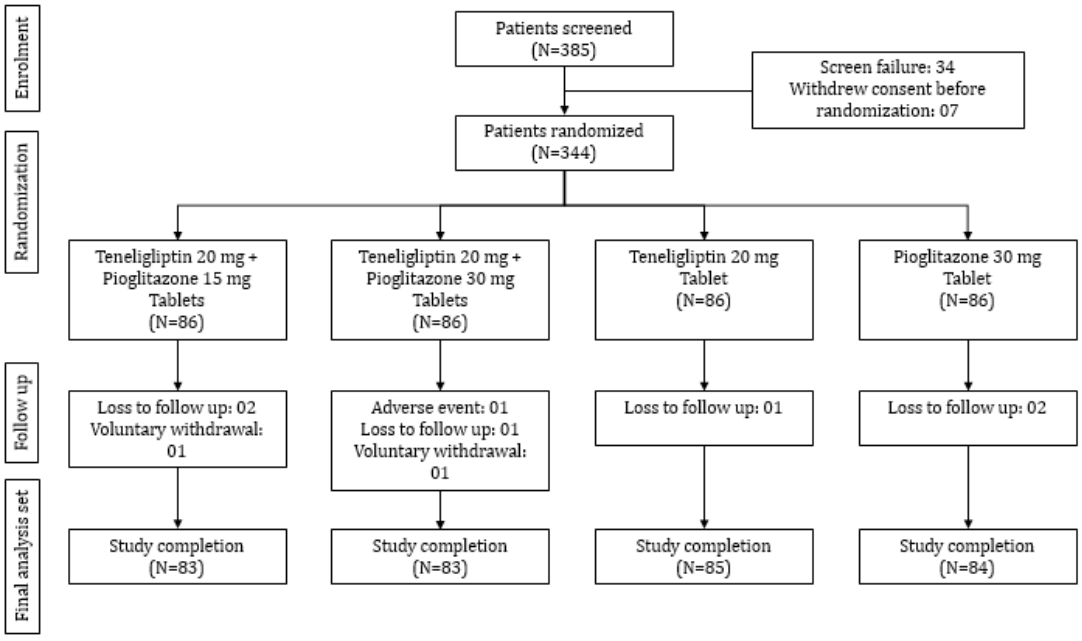

Figure 1: Patient flow diagram

Statistical analysis

The summary statistics were obtained for variables according to the scale of measurement. Continuous variables are expressed in terms of mean and standard deviation, while categorical variables are expressed in terms of percentage. The comparison of demographic and anthropometric parameters across four groups was performed using a one-way analysis of variance, while gender distribution was tested statistically using Pearson's chi-square test. The primary and secondary endpoints were compared between test and reference groups using a t-test for independent samples. The adverse events were summarized according to groups in terms of frequencies and percentages. All the analyses were carried out using SAS 9.4 software and the statistical significance was tested at 5% significance level.

Results

Table 1 provides a summary of baseline demographic and anthropometric characteristics of patients in each group. The difference of means of all parameters across groups was statistically insignificant. The vital, laboratory, and lipid parameters of patients also differed insignificantly across groups at baseline (data not shown). Thus, the treatment groups were comparable at baseline.

Characteristics	Statistics	Teneligliptin 20 mg + Pioglitazone 15 mg Tablets	Teneligliptin 20 mg + Pioglitazone 30 mg Tablets	Teneligliptin Tablets 20 mg	Pioglitazone Tablets 30 mg	P-value
	N	86	86	86	86	
Age (Year)	Mean (SD)	47.41 (8.55)	45.37 (8.86)	45.64 (9.45)	44.74 (9.00)	0.2453*
Male	n (%)[1]	46 (13.37%)	48 (13.95%)	49 (14.24%)	44 (12.79%)	0.8752†
Female	n (%)[1]	40 (11.63%)	38 (11.05%)	37 (10.76%)	42 (12.21%)	
Height (Cm)	Mean (SD)	163.43 (7.20)	161.98 (7.02)	163.83 (7.36)	162.45 (7.66)	0.3187*
Weight (Kg)	Mean (SD)	66.38 (9.80)	66.60 (9.80)	67.15 (10.57)	66.35 (10.44)	0.9518*
BMI (Kg/m^2)	Mean (SD)	24.78 (2.75)	25.32 (2.97)	24.94 (3.07)	25.08 (3.09)	0.6801*

*Obtained using one-way ANOVA, †Obtained using Pearson's chi-square test; $P < 0.05$ is considered as statistically significant; 1Percentage obtained with reference to total sample size

Table 1: Demographic characteristics by treatment group

The primary efficacy endpoint HbA_1c was analysed in each group at baseline, week 12 and week 24 (Table 2). Pair-wise comparisons were performed between teneligliptin + pioglitazone combination, and each of the monotherapies. At baseline, the mean HbA_1c across all the groups was insignificantly different. At week 12, the mean reduction in HbA_1c in FDC of teneligliptin 20 mg + pioglitazone15 mg group was -1.32 ± 0.78%, and was significantly more (in absolute form) than teneligliptin 20mg alone (-0.87 ± 0.32%), as well as pioglitazone 30mg alone (-0.91 ± 0.40%) with $p < 0.0001$ each. Whereas at week 24, the mean HbA_1c change was significantly more (in absolute form) for FDC of teneligliptin 20 mg + pioglitazone 15 mg group (-1.36 ± 0.81%) as compared to teneligliptin 20 mg (-0.89 ± 0.33%) and pioglitazone 30 mg (-0.93 ± 0.42%) with $p < 0.0001$ each. On similar lines, comparison was performed between FDC of teneligliptin 20 mg + pioglitazone 30mg group and respective monotherapies. The mean change in HbA_1c in FDC of teneligliptin 20 mg + pioglitazone 30 mg group was -1.53 ± 0.75%, and was significantly more (in absolute form) than teneligliptin 20 mg alone, as well as pioglitazone 30mg alone with $p < 0.0001$ each at week 12. At week 24, the mean reduction in FDC of teneligliptin 20mg + pioglitazone 30 mg group was -1.57 ± 0.75%, and was significantly more (in absolute form) as compared to teneligliptin 20mg and pioglitazone 30 mg groups with $p < 0.0001$ each.

Visit	Statistics	Teneligliptin 20 mg + Pioglitazone 15 mg Tablets (A) (n=83)	Teneligliptin 20 mg + Pioglitazone 30 mg Tablets (B) (n=83)	Teneligliptin Tablets 20 mg (C) (n=85)	Pioglitazone Tablets 30 mg (D) (n=84)	*P*-value* (A vs C)	*P*-value* (A vs. D)	*P*-value* (B vs C)	*P*-value* (B vs. D)
Baseline	Mean (SD)	8.71 (0.80)	8.67 (0.73)	8.66 (0.81)	8.66 (0.79)	0.6692	0.6806	0.9207	0.9376
Week 12	Mean (SD)	7.39 (0.87)	7.14 (0.76)	7.79 (0.80)	7.75 (0.77)	**0.0022**	**0.0048**	**< 0.0001**	**< 0.0001**
Change: Baseline to Week12	Mean (SD)	-1.32 (0.78)	-1.53 (0.75)	-0.87 (0.32)	-0.91 (0.40)	**< 0.0001**	**< 0.0001**	**< 0.0001**	**< 0.0001**
Week 24	Mean (SD)	7.34 (0.88)	7.10 (0.73)	7.78 (0.80)	7.72 (0.77)	**0.0009**	**0.0034**	**< 0.0001**	**< 0.0001**
Change: Baseline to Week 24	Mean (SD)	-1.36 (0.81)	-1.57 (0.75)	-0.89 (0.33)	-0.93 (0.42)	**< 0.0001**	**< 0.0001**	**< 0.0001**	**< 0.0001**

*Obtained using t-test for independent samples; $P < 0.05$ is considered as statistically significant

Table 2: Descriptive statistics for glycosylated haemoglobin [HbA1c (%)] and its change from baseline to different time points in each study group

The secondary endpoint, fasting blood glucose (FBG) was analysed on similar lines with the results shown in Table 3. At baseline, the mean FBS level in all the four study groups was comparable. At week 12, FBG levels showed that the mean change in FDC of teneligliptin 20 mg + pioglitazone 15 mg group (-37.77 ± 15.99 mg/dl) was significantly more (in absolute form) than teneligliptin 20mg (-22.58 ± 13.07 mg/dl) and pioglitazone 30mg (-27.69 ± 13.51 mg/dl) with $p < 0.0001$ each. The mean change in FDC of teneligliptin 20 mg + pioglitazone 30mg group (-44.73 ± 20.69 mg/dl) was also statistically significant ($p < 0.0001$), when compared with individual drug groups. Similar significant reductions in FBG were seen in both FDC groups at week 24 with $p < 0.0001$, when compared to individual drug groups.

Parameter	Visit	Teneligliptin 20 mg + Pioglitazone 15 mg Tablets	Teneligliptin 20 mg + Pioglitazone 30 mg Tablets	Teneligliptin Tablets 20 mg	Pioglitazone Tablets 30 mg	*P*-value* (A vs. C)	*P*-value* (A vs. D)	*P*-value* (B vs. C)	*P*-value* (B vs. D)
		(A)	**(B)**	**(C)**	**(D)**				
		(n=83) Mean (SD)	**(n=83)** Mean (SD)	**(n=85)** Mean (SD)	**(n=84)** Mean (SD)				
Fasting Blood Glucose (mg/dL)	Baseline	174.97 (19.05)	178.02 (19.30)	176.03 (18.12)	175.52 (18.69)	0.7091	0.847	0.4865	0.3904
	Change: Baseline to Week 12	-37.77 (15.99)	-44.73 (20.69)	-22.58 (13.07)	-27.69 (13.51)	< 0.0001	< 0.0001	< 0.0001	< 0.0001
	Change: Baseline to Week 24	-38.60 (15.13)	-45.41 (20.66)	-23.29 (14.33)	-29.65 (14.76)	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Post-prandial Blood Glucose (mg/dL)	Baseline	268.24 (43.43)	267.40 (46.55)	261.30 (44.16)	261.66 (40.27)	0.3003	0.3043	0.3795	0.3885
	Change: Baseline to Week 12	-77.38 (6.77)	-82.10 (10.65)	-60.61 (6.94)	-39.38 (11.45)	< 0.0001	< 0.0001	< 0.0001	< 0.0001
	Change: Baseline to Week 24	-76.72 (7.16)	-81.50 (4.41)	-60.13 (6.88)	-39.03 (12.76)				

*Obtained using t-test for independent samples; $P < 0.05$ is considered as statistically significant

Table 3: Descriptive statistics for blood glucose parameters and their change from baseline to different time points in each study group.

The 2-hr Post-Prandial Blood Glucose (PPBG) data is also shown in Table 3. The baseline differences in mean PPBG levels were statistically insignificant across all groups. The mean change in PPBG at week 12 in both FDC was significantly more when compared with individual drug groups with $p < 0.0001$ each. The mean change at week 24 in FDC of teneligliptin 20 mg + pioglitazone 15mg group was -76.72 ± 7.16 mg/dl, in teneligliptin 20mg alone was -60.13 ± 6.88 mg/dl and pioglitazone 30 mg alone was-39.03 ± 12.76 mg/dl, and the comparison of FDC with both individual drug groups showed statistical significance with $p < 0.0001$. Similar significant change was seen in FDC of teneligliptin 20 mg + pioglitazone 30 mg group (-81.50 ± 4.41 mg/dl), when compared with individual drugs alone at week 12 and week 24 ($p < 0.0001$).

Additionally, the number of patients attaining HbA_1c less than 7% (ADA goal) at the end of study was determined in each treatment group (Figure 2) [21]. The proportion was maximum in teneligliptin 20mg + pioglitazone 30 mg group (55.4%), followed by teneligliptin 20 mg + pioglitazone 15 mg group with 49.4%, pioglitazone 30 mg with 29.8% and teneligliptin 20 mg with 25.9%. The difference of proportions between dual therapy and monotherapy groups were statistically significant ($p < 0.05$).

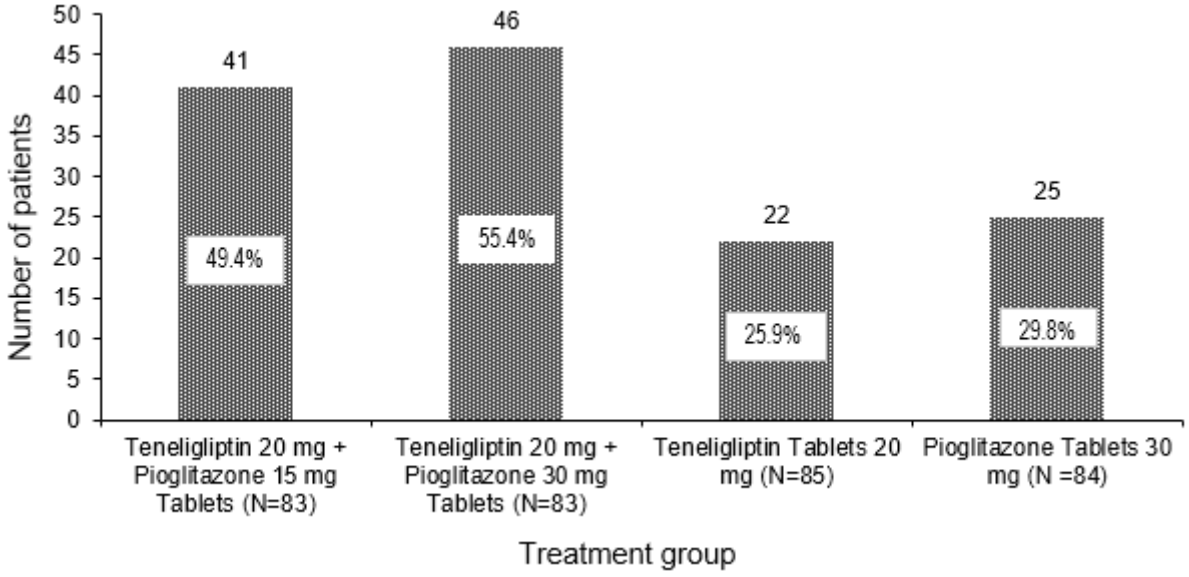

Figure 2: Number of patients achieving HbA1c < 7% at the end of study (Week 24)

As regards to safety evaluation, hypoglycaemia was observed in 3.48% of cases treated with dual therapy, while 1.74% with monotherapy. All hypoglycaemia episodes were of mild severity. Weight gain was observed in 1.74% of the patients in a dual therapy group, while 2.32% in the pioglitazone monotherapy group. All other adverse events were mild to moderate in nature. All the events were followed up until they were completely resolved. No serious AE was reported during the study.

Discussion

The interest of this study was to determine the efficacy, safety and tolerability of FDC of teneligliptin 20 mg + pioglitazone 15/30 mg in comparison to monotherapy of teneligliptin 20 mg and pioglitazone 30 mg in type 2 diabetic patients uncontrolled on metformin monotherapy. The glycaemic parameters like HbA1c, FBG and PPBG were assessed at baseline, week 12, and the end of treatment (week 24). The change in these parameters were compared to baseline to understand the efficacy of combination therapy against monotherapy. American Diabetic Association guidelines have recommended lifestyle management as the primary treatment for T2DM, and metformin as the preferred anti-hyperglycaemic agent. However, complete glycaemic control with monotherapy is often a challenge. One recent study using teneligliptin, as an add-on to conventional therapy, has shown improved glycaemic control in T2DM patients [22]. Teneligliptin, a DDP-4 inhibitor, increases the levels of active glucagon-like peptides (GLP-1) and thus indirectly promotes insulin secretion and beta-cell sensitivity to glucose. Preserving β-cell function is essential for sustained glycaemic control and animal studies have shown that DPP-4i have the ability to preserve the architecture of pancreatic islets and β-cell mass [19]. Pioglitazone, the most potent insulin sensitizer, improves peripheral uptake of glucose. Kodawaki and Kondo (2013) performed a study using a combination of teneligliptin + pioglitazone and compared its efficacy with placebo + pioglitazone on glycaemic parameters in Japanese T2DM patients [23]. They observed a significant reduction in HbA_1c with teneligliptin as an add-on to pioglitazone, against placebo. In our study also, we observed a significant reduction in HbA_1c levels in teneligliptin 20 mg + pioglitazone 15 mg and teneligliptin 20 mg + pioglitazone 30 mg groups as compared to teneligliptin 20mg alone and pioglitazone 30mg alone groups. In addition, the dual therapy showed a significant reduction in fasting and post-prandial blood glucose compared to either monotherapy. Similar was the observation in the study by Kodawaki and Kondo (2013). The recent TREAT-INDIA2 study on 10,623 Indian type 2 DM patients has shown a significant improvement in glycaemic control using teneligliptin as add-on to other anti-diabetic drugs [24]. From pathophysiological perspective, the combination of teneligliptin and pioglitazone acts in a synergistic manner by enhancing insulin secretion and suppressing glucagon release, improving incretin gut effects, enhancing insulin-mediated glucose utilization in peripheral tissues and restraining lipolysis. The combination has the potential for sustained glycaemic control with good safety and tolerability profile [20]. Moreover, the PROactive study showed that pioglitazone reduces the risk of macrovascular events in high-risk type 2 diabetes patients [25]. Thus, the combination has

pleotropic benefits as well.

Conclusion

The present study demonstrated that type 2 DM patients, inadequately controlled on metformin and having higher HbA1c showed synergistic, superior and significant control of glycaemic parameters with a fixed dose combination therapy of teneligliptin 20 mg + pioglitazone 15 mg as well teneligliptin 20 mg + pioglitazone 30 mg, as compared to either of monotherapies, teneligliptin and pioglitazone. The combination of teneligliptin + pioglitazone did not increase the incidence of hypoglycaemia, and did not substantially worsen the weight-gain induced by Pioglitazone. The vital, lipid, hematological and biochemical parameters showed negligible changes from baseline to end of study in all the treatment groups, and the combination was well tolerated.

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