Original Article

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Real-world Retrospective Assessment of Initiation and Effectiveness of Dual Combination Therapy with Metformin and Teneligliptin in Drug Naïve Indian Type 2 Diabetes Mellitus Patients (INITIATE)

Internal Medicine Section

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ABSTRACT

Introduction: Diabetes Mellitus (DM) has become the leading health concern worldwide over the last few decades. But despite advances in both understanding of the pathophysiology of Type 2 Diabetes Mellitus (T2DM), and the development of new treatment strategies, current management of patients with T2DM remains suboptimal. Initial monotherapy is frequently inadequate in patients with high baseline Glycated Haemoglobin (HbA1c). Thus, initial combination therapy has emerged as an alternative approach.

Aim: To assess INItiation and effecTiveness of dual combInation therapy with metformin And Teneligliptin in drug naïvE T2DM patients (INITIATE).

Materials and Methods: In this retrospective, multicentre study, newly diagnosed drug naïve T2DM patients failed with diet and exercise prior to screening and initiated with dual therapy of metformin and teneligliptin were enrolled. Data of all the patients prescribed with any therapeutic dose of metformin (250 mg, 500 mg, 750 mg, 1000 mg, 1500 mg, 2000 mg) and teneligliptin (20 mg, 40 mg) was considered. The data was analysed to assess change in glycaemic parameters from baseline to 12 weeks. Paired t-test was applied for statistical results.

Results: Data of 7857 patients were analysed. The mean change of Fasting Plasma Glucose (FPG) from baseline {202.29±52.2 mg/dL (11.23±2.89 mmol/L)} to 12 weeks {142.57±34.5 mg/dL (7.91±1.91 mmol/L)} was -59.72±17.7 mg/dL (-3.31±0.98 mmol/L) (p-value <0.0001). The absolute change in mean Postprandial Plasma Glucose (PPG) from baseline {(286.26±80.43 mg/dL (15.89±4.46 mmol/L)} to 12 weeks {(198.30±42.24 mg/dL (11±2.34 mmol/L)} was -87.96±38.19 mg/dL (-4.88±2.12 mmol/L) (p-value <0.0001). Mean HbA1c level was 8.11%±1% (65±10.9 mmol/mol) at baseline and decreased significantly to 7.15%±0.94% (55±10.3 mmol/mol) (p-value <0.0001) with a mean change of -0.96±0.06 (-10.5±0.7 mmol/mol) at 12 weeks. Total 42.83% (n=3365) patients achieved target HbA1c (<7%) at 12 weeks.

Conclusion: Initiation of dual therapy with metformin and teneligliptin in drug naïve Indian T2DM patients significantly improved glycaemic control.

Keywords: Dual therapy, Glycated haemoglobin, Initial combination treatment

INTRODUCTION

Diabetes Mellitus (DM) has become the leading health concern worldwide over the last few decades. The prevalence of DM has increased from 108 million (4.7%) in 1980 to 425 million (9.3%) in 2019, and it is estimated to be 700 million (10.9%) by 2045 [1,2]. Type 2 Diabetes (T2DM) is the most prevailing form of diabetes which encompasses 90-95% of the diagnosed DM [2]. It is a progressive metabolic disorder characterised by increasing hyperglycaemia resulting from defects in insulin secretion, insulin action or both [3]. Hyperglycaemia is associated with a wide range of microvascular and macrovascular complications. To reduce these complications, targeted glycaemic control is recommended [4].

There is robust evidence indicating that achieving HbA1c targets reduces the risk of complications of T2DM. Further, there is also potential benefit in achieving HbA1c targets as soon as possible [5]. Despite advances in both understanding of the pathophysiology of T2DM and the development of new treatment strategies, current management of patients with T2DM remains suboptimal [6].

According to American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), hypoglycaemic monotherapy is usually recommended as an initial treatment strategy in newly diagnosed T2DM patients [7]. However, initial monotherapy is frequently insufficient to achieve or maintain glycaemic targets [8]. Thus, initial combination therapy has emerged as an alternative approach. The ADA "Standards of Medical Care in Diabetes" recommends considering initiating dual therapy in patients with newly diagnosed T2DM who have HbA1c ≥1.5% (12.5 mmol/mol) above their glycaemic target [7]. Additionally, the latest American Association of Clinical Endocrinologists' (AACE) treatment algorithm recommended that patients with HbA1c level of >7.5% should receive combination therapy with metformin plus an additional drug [9].

Previous studies have demonstrated that teneligliptin, a Dipeptidyl Peptidase-4 Inhibitor (DPP4I), was effective with a significant reduction in glycaemic parameters as an add-on therapy for inadequately controlled T2DM patients who are already on regimen of diet, exercise, and the maximal tolerable dose of metformin monotherapy [10,11]. There is need for evidence regarding the effectiveness of initial dual combination of metformin and teneligliptin in Indian drug naive T2DM patients. Hence, the current study was intended to assess the initiation and effectiveness (improvement in glycaemic parameters) of metformin in combination with teneligliptin initiated as a dual combination therapy in drug naïve T2DM patients in Indian population.

MATERIALS AND METHODS

This was a retrospective multicentric study. Physicians with experience of treating T2DM for more than five years and who had data available as per protocol in their clinics/hospitals and willing to

share were considered across the country. The data was provided by respective sites (210 clinics/hospitals) in a uniform case report form format, which was then entered in a central data base. Data collection was started after getting approval from Suraksha Ethics Committee, Asian Institute of Medical Sciences, Dombivili, Mumbai, India. {Registration No (ECR/644/Inst/MH/2014/RR-17) and OHPP No IORG0008323 dated 9/5/19}. Suraksha Ethics Committee is an institutional committee which provides approval to study protocols involving multiple independent centres.

The data was obtained from hospital database across four zones of India between June 2019 to December 2019. Since this was a retrospective study, authors planned to capture and analyse the data of maximum possible patients from the selected centres. A total of 7857 patients' records were retrieved in this study to assess the effectiveness of initial dual combination therapy with metformin and teneligliptin in newly diagnosed drug naïve T2DM patients. Data of patients prescribed with any therapeutic dose of metformin (250 mg, 500 mg, 750 mg, 1000 mg, 1500 mg, 2000 mg) and teneligliptin (20 mg, 40 mg) was considered.

Inclusion criteria: Patients of either gender ≥18 years of age with newly diagnosed drug naïve T2DM who had failed treatment with diet and exercise prior to screening and initiated with dual drug combination of metformin plus teneligliptin were included in the study. All the centres having data available as per protocol were considered in this study.

Exclusion criteria: Patients with type 1 diabetes, patients initiated on insulin therapy, pregnant or lactating females were excluded from the study. Patients with serious diabetic and cardiovascular conditions were excluded from the study.

Patients were required to have readings of Fasting Plasma Glucose (FPG), Post-Prandial Plasma Glucose (PPG) and HbA1c at baseline and at 12 weeks. The effectiveness parameters considered in this study were FPG, PPG and HbA1c. Since 12 weeks is the minimum time duration to expect any significant change in HbA1c, this was the duration considered for assessment of effectiveness [3]. For each patient, the following information was collected regarding age, gender, Body Mass Index (BMI), FPG, PPG and HbA1c. The glycaemic parameters were evaluated to determine the change at 12 weeks compared to baseline.

STATISTICAL ANALYSIS

All statistical analyses were done using the software STATA. All characteristics were summarised descriptively. For continuous variables, data was represented using mean±Standard Deviation (SD). For categorical data, number and percentages were used in the data summaries. The difference between the means of analysis variables between the two independent groups were tested using paired t-test. All p-values were two-tailed and values were considered statistically significant if p-value <0.05.

RESULTS

A total of 7857 patient's data was retrieved and analysed. Among all patients, 62.64% were males and the mean age of the enrolled patients was 51.56±10.89 years. [Table/Fig-1] presents the demographic characteristics of the patients. The mean body weight of the study population was 69.37 kg at baseline and 68.06 kg at 12 weeks follow-up. The mean BMI was observed to be 26.10 kg/m^2 at baseline and 25.62 kg/m^2 at 12 weeks follow-up.

[Table/Fig-2] presents the summary of changes in glycaemic parameters from baseline to 12 weeks with the use of dual drug combination of metformin and teneligliptin. Among all patients, there was a significant reduction in mean FPG {-59.72±17.7 mg/dL (-3.31±0.98 mmol/L)}, PPG {-87.96±38.19 mg/dL (-4.88±2.12 mmol/L)} and HbA1c {-0.96±0.06 (-10.5±0.7 mmol/mol)} from baseline to 12 weeks (p-value <0.0001). Among all patients, 42.83% achieved the target HbA1c (<7%) at 12 weeks.

Parameters		Values (Mean±SD)
Age (years)		51.56±10.89
Gender n (%)	Males	4922 (62.64%)
	Females	2935 (37.36%)
Height (cm)		163.51±8.26
Body weight (kg)		69.37±9.97
BMI (kg/m^2)		26.10±4.42

[Table/Fig-1]: Summary of patient demographics at baseline.
N=7857, SD: Standard Deviation

Variables	FPG (mg/dL) (Mean±SD)	PPG (mg/dL) (Mean±SD)	HbA1c (mg/dL) Mean±SD
Baseline visit	202.29±52.2	286.26±80.43	8.11±1
Follow-up visit (12 weeks)	142.57±34.5	198.30±42.24	7.15±0.94
Absolute change from baseline	-59.72	-87.96	-0.96
p-value*	≤0.0001	≤0.0001	≤0.0001
Proportion of patients achieving the target HbA1c (<7%) at 12 weeks			3365 (42.83%)

[Table/Fig-2]: Summary of changes in glycaemic parameters from baseline to 12 weeks.
FPG: Fasting plasma glucose, PPG: Postprandial plasma glucose, HbA1c: Haemoglobin A1c, SD: Standard deviation; *Paired t-test

Regarding the dosages of study drugs, due to the retrospective nature of study, data of all the patients prescribed with any therapeutic dose of metformin and teneligliptin was considered including the patients in whom doses were modified during the study period. The patients only on dual combination of metformin and teneligliptin were considered in the study.

DISCUSSION

The database analysis of this study revealed the effectiveness of dual combination therapy with metformin and teneligliptin in drug naïve Indian T2DM patients. The results showed that initiation of metformin and teneligliptin as a dual combination therapy was significantly effective in improving FPG, PPG and HbA1c from baseline to 12 weeks. Most common combination prescribed as initial treatment in this study was metformin 500 mg plus teneligliptin 20 mg (85.61%) followed by metformin 1000 mg plus teneligliptin 20 mg (10.51%).

In a recent phase 3, randomised, double-blind, placebo-controlled study, Ji L et al., found that addition of teneligliptin 20 mg in T2DM patients with metformin dose ≥1000 mg/day, yielded significant reductions in HbA1c (-0.81%; p-value <0.0001) and FPG (-22.2 mg/dL; p-value <0.0001) at week 12. At week 24, 41.7% patients on teneligliptin achieved HbA1c <7% compared to 16.1% patients on placebo (p-value <0.0001) [12].

Bryson A et al., conducted a double-blind, parallel group study investigating the efficacy and tolerability of teneligliptin with dose of 5, 10, 20 or 40 mg as an add-on in 447 T2DM patients who were inadequately controlled with stable metformin monotherapy ≥1000 mg/day. From baseline to 12 weeks, HbA1c was reduced by -0.65% and -0.81% (both p-value <0.0001) with 20 and 40 mg doses of teneligliptin, respectively [13].

In a 16-week trial, Kim MK et al. reported that teneligliptin 20 mg/day compared to placebo as an add-on to metformin ≥1000 mg/dL was associated with significantly greater reductions in HbA1c {adjusted mean changes from baseline values were -0.90% for teneligliptin plus metformin compared with -0.12% for placebo plus metformin (p-value <0.0001)} and FPG {adjusted mean change in FPG from baseline to week 16 was -16.79 mg/dL for teneligliptin plus metformin versus +5.69 mg/dL for placebo plus metformin (p-value <0.0001)} in T2DM patients [14].

A retrospective analysis was carried out by Chudasama DB et al., to assess the efficacy of teneligliptin with metformin in 450 drug naïve

Indian T2DM patients. Reduction in HbA1c from baseline was 1.2%, 1.6% and 1% at 12, 24 and 48 weeks, respectively. Around 66% of subjects were seen with HbA1c <7% at 24 weeks. Study concluded that the combination of teneligliptin 20 mg with metformin 1000 mg was associated with clinically significant reduction in HbA1c [15].

In a prospective, parallel-group, open-label comparative study, Nishanth T et al., compared dual therapy of glimepiride 1 mg plus metformin 500 mg once daily (group A), with teneligliptin 20 mg plus metformin 500 mg once daily (group B) over three months. The reductions in HbA1c, FPG and PPG were 0.84% (p=0.002), 33.3 mg/dL (p-value <0.001), 79.93 mg/dL (p=0.002) and 1.18% (p=0.001), 44 mg/dL (p-value<0.001), 75 mg/dL (p-value=0.002), respectively in group A and group B [16].

In a large real world retrospective study conducted by Ghosh S et al., the effectiveness of teneligliptin was assessed in improving glycaemic control among Indian patients with T2DM. Out of 10,623 enrolled patients, 4299 were on teneligliptin and metformin combination therapy. This dual therapy reduced FPG, PPG and HbA1c from 160.71±23.06 mg/dL, 266.31±47.40 mg/dL and 8.56±1.15% at baseline to 119.21±22.02 mg/dL, 178.92±43.57 mg/dL and 7.8±1.28% at 12 weeks. The difference was -41.5 mg/dL, -87.39 mg/dL and -0.76% in FPG, PPG and HbA1c respectively (p-value <0.0001) [17].

Another large real-world retrospective data was analysed by Ghosh S et al., to assess the efficacy of teneligliptin in Indian T2DM patients. This study enrolled 4305 patients, out of which 1028 patients were prescribed teneligliptin and metformin combination therapy. Significant reductions in HbA1c, FPG and PPG by -1.07%, -44.72 mg/dL and -69.58 mg/dL respectively were seen in patients receiving this combination therapy at the end of 12 weeks (p-value <0.0001) [18].

In treatment of diabetes, there is often some complacency for physicians as well as patients due to the lack of symptoms at the early stage. Hence, to achieve optimal glycaemic targets, combination therapy of two drugs having complementary mechanisms of action to target different physiological abnormalities may be required. The United Kingdom (UK) Prospective Diabetes Study (UKPDS) has proved that monotherapy does not provide long-term stable glycaemic control, emphasising the need of combination therapy. Thus, early combination therapy holds the promise of altering the course of disease, which provides long-term stable HbA1c levels and also delays the need for therapy intensification [19].

Metformin acts by enhancing insulin sensitivity and affects fasting plasma insulin concentrations. It lowers blood glucose and insulin levels by reducing hepatic glucose output while posing minimal risk of hypoglycaemia and weight gain [20]. Teneligliptin is a potent, third-generation, competitive, reversible inhibitor of DPP-4 and decreases the degradation of Glucagon Like Peptide 1 (GLP-1), consequently stimulating insulin secretion and suppressing glucagon secretion in a glucose-dependent manner. Combinations of DPP-4 inhibitors and metformin results in increasing concentrations of active GLP-1 which has an insulinotropic effect and glucagonostatic actions that can augment postprandial insulin secretion, resulting in glucose lowering effect [12]. Dual drug therapy of metformin plus teneligliptin is one of the most commonly used combinations in Indian clinical practice. This can reflect the change in prescribing habits of medical practitioners, possibly adopting the safer option of gliptins. As a result of emergence of many gliptins and availability of affordable teneligliptin in India, it has greater impact on glycaemic control in newly diagnosed T2DM [18].

Limitation(s)

Retrospective design is one of the limitations of this study, which does not allow to determine a cause-and-effect relationship due to limited availability of the details of medical records. The safety assessment and comparative analysis was not possible as this was a single arm study focused on effectiveness of teneligliptin plus metformin combination.

CONCLUSION(S)

This study provides the evidence of significant improvement in glycaemic parameters with the initiation of dual combination therapy with metformin and teneligliptin in newly diagnosed drug naïve T2DM patients in India. Metformin plus teneligliptin combination may be a good choice as initial dual therapy in drug naïve Indian T2DM patients. Large sample size (7857 T2DM patients) is the biggest strength of the present study. It also makes this study probably the largest real-world data assessing teneligliptin plus metformin dual combination as initial treatment in drug naïve Indian T2DM patients.

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