Original Research Article

Role of teneligliptin in rural India as add-on third drug in patients with type 2 diabetes mellitus

Chandra Narayan Gupta[1]*, Vijay Raghavan[2], Sukanta Sen[3], Sanjay Kothari[4]

[1]Department of General Medicine, ICARE Institute of Medical Sciences and Research, Banbishnupur, P.O. Balughata, Purba Medinipur, Haldia, West Bengal- 721645, India
[2]Department of Community Mediicne, ICARE Institute of Medical Sciences and Research, Banbishnupur, P.O. Balughata, Purba Medinipur, Haldia, West Bengal- 721645, India
[3]Department of Pharmacology, ICARE Institute of Medical Sciences and Research, Banbishnupur, P.O. Balughata, Purba Medinipur, Haldia, West Bengal- 721645, India
[4]Department of Radiology, ICARE Institute of Medical Sciences and Research, Banbishnupur, P.O. Balughata, Purba Medinipur, Haldia, West Bengal- 721645, India

*Correspondence:
Dr. Chandra Narayan Gupta,
E-mail: cnarayangupta@gmail.com

ABSTRACT

Background: Teneligliptin was introduced in India in May 2015. It has gained popularity and is already widely prescribed in type 2 diabetes mellitus (T2DM). The main aim of our study was to assess the efficacy and superiority of teneligliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor as add-on third drug along with metformin and glimepiride in the treatment of type 2 diabetes mellitus in rural India.
Methods: In this comparative observational study, three groups of uncontrolled type 2 diabetes (on monotherapy) patients each comprising 50 in number were studied for 3 months. Groups were divided into patients on triple drug regimens (Group A- Metformin+Glimepiride+voglibose; Group B- Metformin+Glimepiride+Pioglitazone and Group C- Metformin+Glimepiride+Teneligliptin). In each group FBS and PPBS were tested at the beginning and at 4 weeks intervals. HbA1c was tested at the start of study and at the end of 12 weeks.
Results: After 12 weeks of therapy, it was observed that FBS, PPBS and HbA1c were significantly reduced in Group-C patients containing teneligliptin in comparison to Group-A and B containing voglibose and pioglitazone respectively.
Conclusions: Teneligliptin significantly improves glycemic control in Indian patients with T2DM when prescribed as an add-on to one or more other commonly prescribed antidiabetic drugs, even in patients of rural India. It may be an ideal add-on third drug in the treatment of T2 DM patients.

Keywords: DPP-4 inhibitor, Glycemic control, Teneligliptin, Type 2 diabetes mellitus

INTRODUCTION

The prevalence of type 2 diabetes mellitus is increasing globally. Diabetes mellitus is one of the most challenging health problems of the 21st century. Around 8.8% of adults are estimated to have diabetes. About 75% live in low and middle income countries. As per the International Diabetes Federartion (IDF) 2015 report, India is harbouring 69.2 million Diabetes patients, second only to china (109.6 million).[1,2]

Whenever we are treating a case of T2DM, according to the latest ADA guidelines we first of all advice diet and lifestyle modification. If the blood sugar is not controlled,

we advise the standard and safest molecule metformin in full therapeutic dose. Indication of metformin as per American Diabetic Association (ADA) guideline is "it is to be given in all T2DM patients in absence of containdications".[3] It does not cause hypoglycaemia and helps to reduce body weight. It is contraindicated in renal impairment and rarely may cause lactic acidosis.[4]

If the blood sugar is not controlled we add a second drug like glimepiride which is a second generation sulfonylurea, cheap, effective and widely available drug. We have to observe for hypoglycaemia. If then the blood sugar is not controlled we search for a third drug.

There are several options. Voglibose is an alpha glucosidase inhibitor which slows intestinal carbohydrate absorption and reduce postprandial blood sugar. Side effects like flatulence and diarrhoea are common. Pioglitazone increases insulin sensitivity and thus reduce blood sugar. But it has the danger of weight gain, edema, heart failure and bone fracture. Here lies the importance of gliptins particularly teneligliptin which inhibits DPP-4 and thus increase incretin hormones like glucagon like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) in the intestine. These incretins increase insulin from beta cells and decrease glucagon from alpha cells of pancreas in a glucose dependent manner- thereby decrease the blood sugar level. It is a very effective and safe drug with no chance of hypoglycaemia. Teneligliptin, a third-generation gliptin offers unique pharmacodynamic property with unique "J-shaped anchor- lock domain" which provides potent and long duration of action.[5] Efficacy and safety of teneligliptin has been established in Japanese and Korean populations in several randomized controlled trials with limited sample size.[6] Comparable efficacy between gliptins and sulfonylurea when either is added to metformin has been proved in different meta-analyses.[7,8]

DPP-4 inhibitors inhibit degradation of native GLP-1 and thus enhance the incretin effect.[9] Other desirable actions of GLP-1 are to delay gastric emptying, thereby dampening post prandial hyherglycemic excursions, and to promote satiety and inhibit energy intake, perhaps preventing weight gain and encouraging weight loss.[10]

The glycemic efficacy was assessed by analyzing the mean change in values of glycosylated hemoglobin (HbA1c), FPG, and PPG from baseline following combination antidiabetic therapy and compared with teneligliptin based combination therapy.

METHODS

This randomized parallel group observational study was conducted in a tertiary care teaching hospital, Haldia, Purba Medinipur, West Bengal, India from January 2016 to June 2016 after taking institutional ethics committee permission. Total duration of study was 12 weeks.

Predesigned structured proforma was used to capture data from the prescribing for the present combination antidiabetic drugs on type 2 diabetes patients. Information collected included demographic data, antidiabetic medications, and glycemic status of the patient at the time of initiation and after 3 months of combination antidiabetic therapy.

FBS and PPBS were tested at every 4 weeks intervals. HbA1c was done at the start of study and at the end of 12 weeks. In each patient age, gender, race, body weight, height, BMI, marital status, diagnosis with duration of disease were recorded. Associated medical illnesses like systemic hypertension, bronchial asthma, neurological disorders, and hepatic and renal disorders were noted. Past history of medication for diabetes mellitus were taken. Any drug reaction was carefully noticed.

Inclusion criteria

- Ambulatory subjects who were suffering from type 2 diabetes mellitus and prescribed anti-diabetic drug at medicine OPD
- Subject's age more than 18 years of either sex
- Willing to give informed consent for the study.

Exclusion criteria

- Subject's age less than 18 years
- Subjects not agreeing to participate
- Suffering from any serious disease such as hypertensive emergences, unstable coronary heart disease, acute myocardial infarction, acute left ventricular failure, advanced kidney or liver failure and cerebral stroke
- Any condition resulting in severe learning disability (e.g. brain injury) or unable to comprehend for other reasons.

Descriptive analysis was done for the demographic details. Quantitative data of HbA1c, FPG, and PPG from baseline to 3 months after combination antidiabetic regimen was analyzed by two-tailed paired t-test for data. GraphPad Prism5 (version 5.01) statistical software was used for analysis. Statistical tests were considered significant if P-value was <0.05 at confidence interval of 95%.

RESULTS

Data of 150 patients were available for analysis in the present study. Table 2 shows the baseline demographic and clinical characteristics of the study participants. The mean age of patients was 58.84±10.32 years and out of the entire patient population 66.33% were males and 34.66% were females. Almost 59% (n=150) of patients had comorbid conditions, and hypertension (19.33%), and dyslipidemia (23.33%) being the most common (Table 1).

Table 1: Three groups of patients and their doses under study.

Groups [A/B/C]	Treatment Allotted	No. of the patients in each group
Group [A]	Metformin (2000 mg), Glimepiride (2 mg), Voglibose (0.3 mg)	50
Group [B]	Metformin (2000 mg), Glimepiride (2 mg), Pioglitazone (15 mg)	50
Group [C]	Metformin (2000 mg), Glimepiride (2 mg), Teneligliptin (20 mg)	50

Table 2: Demographic and clinical characteristics of the study participants (n=150).

Patients characteristics	N (Percentage)
Total number of patients	150 (100%)
Gender	
Male	98 (65.33%)
Female	52 (34.66%)
Age	
≤60 years	45 (30%)
>60 years	105 (70%)
FBS	
≤126 mg%	15 (10%)
>126 mg%	135 (90%)
PPBS	
≤200 mg%	28 (18.66%)
>200 mg%	122 (81.34%)
HbA1c	
<7	29 (19.33%)
7-8	45 (30%)
>8	76 (50.66%)
Medication for other co-morbid conditions	
Anti-hypertensive (s)	29 (19.33%)
Statins	35 (23.33%)
Antiplatelet drugs	19 (12.66%)
Drug for hypothyroidism	16 (10.66%)

Table 3: Mean reduction in glycaemic parameters from baseline in three groups.

	Drugs	FBS	PPBS	HbA1C
Group A (n=50)	Metformin + Glimepiride + Voglibose	38±17	59±28	1.5±0.8
Group B (n=50)	Metformin+ Glimepiride+ Pioglitazone	40±20	72±34	1.6±1.0
Group C (n=50)	Metformin+ Glimepiride+ Teneligliptin	46±25	78±37	1.8±1.1

Note: Values are presented as mean ± standard deviation otherwise mentioned. P-value <0.0001 for all glycemic parameters in all subgroups.

The glycaemic efficacy was assessed by analyzing the mean changes in the values of FBS, PPBS and HbA1c from start of therapy to the end of 12 weeks study period.

From Table 3 it is clearly evident that in group-C patients getting teneligliptin along with metformin and glimepiride show the maximum reduction of mean values of FBS (-46±25), PPBS (-78±37) and HbA1c (-1.8±1.1).
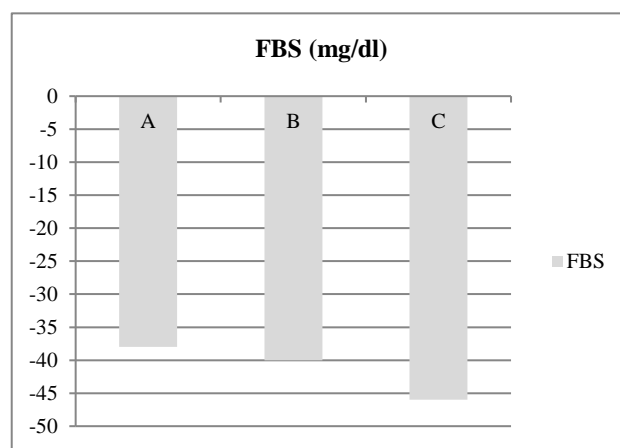

Figure 1: Mean reduction in FBS% in mg/dl.

From this column chart it is obvious that the reduction of fasting blood sugar after 12 week of therapy was greater in Group C, containing teneligliptin compared to group A and B containing voglibose and pioglitazone respectively.
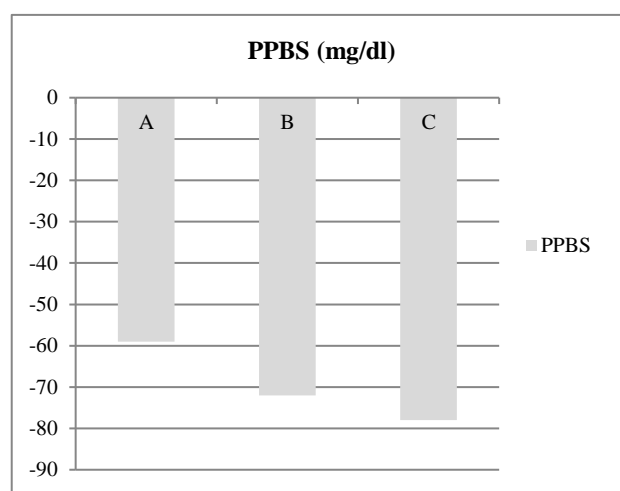

Figure 2: Mean reduction in PPBS% in mg/dl.

From this column chart it is found that 2 hours post prandial blood sugar after 12 week of therapy was significantly reduced in Group C patients getting

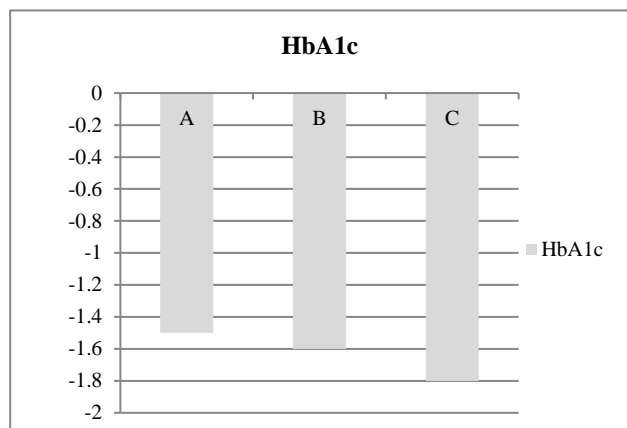tenegligliptin in comparison to Group A and B containing voglibose and pioglitazone respectively.

Figure 3: Mean reduction in HbA1c%.

From this column chart it is observed that after 12 week of therapy there was greater reduction of HbA1c in group C patients containing teneligliptin than the other two groups A and B containing voglibose and pioglitazone respectively.

DISCUSSION

The present comparative study was conducted to assess the efficacy of teneligliptin based regimen with other two combination three drug regimens in rural Indian patients with type 2 diabetes in India. Teneligliptin is usually given 20 mg once daily morning dose and maximum 40 mg can be given. There were no cases of hypoglycemia, weight gain and edema reported in the present study. It is not so costly as compared to other gliptins. It is easily available even in remote areas. No significant drug interactions are there and usually well tolerated. No dose adjustment was needed in patients with renal or hepatic impairment. Teneligliptin can improve endothelial function and reduce renal and vascular oxidative stress in patients with type 2 diabetes mellitus and chronic kidney disease, independently reducing albuminuria or improve in glucose control.

Teneligliptin was seen to be well tolerated and effective in diabetes patients undergoing dialysis.[11] "Cardiovascular safety" is universally seen with all DPP-4 inhibitors. They reduce inflammation by reducing the level of interlukin 6 (IL-6), tumor necrosis factor (TNF-alpha) and Monocyte Chemoattractant Protein-1 (MCP-1).[12] Teneligliptin improves endothelial dysfunction leading to an increase in coronary blood flow of the epicardial and intra-myocardial microcirculation. It also increases adiponectin level, so improves left ventricular diastolic function.[12]

Teneligliptin, a DPP-4 inhibitor was added to the armamentarium for use in patients with type 2 diabetes in India.[2] In different clinical trials conducted in Japan,

Korea, and India, it has been shown to be safe and effective in T2DM patients when used either as monotherapy and combination antidiabetic therapy.[6] It is economical as compared with other gliptins (sitagliptin, saxagliptin, vildagliptin, and linagliptin) available in India.[2]

The average age of the population was >58 years and a significant proportion of patients were above 60 years of age (26.60%). Mean baseline HbA1c level of 8.54% confirms the high prevalence of uncontrolled glycemic status in patients with T2DM patients in developing countries like India.[13] Long-term data from major studies like UK Prospective Diabetes Study has already established the importance of tight and early glucose control to prevent complications of diabetes.[14]

In the teneligliptin monotherapy and combination therapy with other OADs, HbA1c was reduced significantly at 3 months. Similar results were seen with other gliptins like sitagliptin and vildagliptin during real-life observational studies conducted in India and elsewhere.[2, 13-16]

The reduction in glycemic parameters strongly correlated with baseline glycemic values, that is, higher the HbA1c at baseline; higher was the reduction at the end of 3 months. Reduction in FPG and PPG was observed relative to corresponding baseline values. The majority of patients (56%) had one or more comorbid condition like hypertension and dyslipidemia. This high prevalence of comorbid conditions in this study is in accordance with previously reported studies done in India.[2, 17] Patients with co-morbid conditions were on different anti-hypertensives, statins, anti-platelet monotherapy or combination therapy.

CONCLUSION

Teneligliptin provides significant reduction in FBS, PPBs and HbA1c from their baseline values even as combination antidiabetic regimen. It has proven efficacy and safety. So, teneligliptin may be the ideal add on third drug along with metformin and glimepiride in the treatment of type 2 diabetes mellitus. It is found quite effective in patients of rural setting. If there is no question of affordability, then it could be good alternative options as monotherapy or combination anti-diabetic drugs.

REFERENCES

1. International diabetes federation. IDF Diabetes Atlas, 7th ed. Brussels, Belgium: International Diabetes Federation, 2015. Available from:

http://www.diabetesatlas.org. Accessed Jan 27, 2017.

2. Ghosh S, Trivedi S, Sanyal D, Modi KD, Kharb S. Teneligliptin real-world efficacy assessment of type 2 diabetes mellitus patients in India (TREAT-INDIA Study). Diabetes Metab Syndr Obes. 2016;9:347-53.

3. Munjal YP. API textbook of Medicine. 9th Ed. Association of Physicians of India; 341.

4. Rojas LB, Gomes MB. Metformin: an old but still the best treatment for type 2 diabetes. Diabetol Metab Syndr. 2013;5(1):6.

5. Maladkar M, Sankar S, Kamat K. Teneligliptin: Heralding change in type 2 Diabetes. J Diabetes Mellitus. 2016;6(2):113-31.

6. Scott LJ. Teneligliptin; a review in type 2 diabetes. Clin Drug Investig. 2015;35(11);765-72.

7. Deacon CF, Lebovitz HE. Comparative review of dipeptidyl peptidase-4 inhibitors and sulphonylureas. Dia Obes Metab. 2016;18(4):333-47.

8. Foroutan N, Muratov S, Levine M. Safety and efficacy of dipeptidyl peptidase-4 inhibitors vs Sulfonylurea in metformin–based combination therapy for type-2 diabetes mellitus: Systematic review and metaanalysis. Clin Invest Med. 2016;39(2):E48-62.

9. Fauci K, Longo H, Loscalzo J. Harrison's principles of internal medicine 19th Ed. 2015;2:2415.

10. Scheen AJ. A Review of Gliptins in 2011. Expert Opinion on Pharmacotherapy. 2012;13:81-99.

11. Morishita R, Norkagami H, Teneligliptin: Expectations for its pleiotropic action. Expert Opin Pharmacother. 2015;16(3):417-26.

12. Chandalia HB. RSSDI Text book of diabetes mellitus 3rd Ed. Jaypee Digital; 2014:552.

13. Mathieu C, Barnett AH, Brath H. Effectiveness and tolerability of second-line therapy with vildagliptin vs. other oral agents in type 2 diabetes: a real-life worldwide observational study (EDGE). Int J Clin Pract. 2013;67(10):947-56.

14. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359(15):1577-89.

15. Saglietti G, Placentino G, Schellino A. Observational study on dipeptidyl peptidase-4 inhibitors: a real-life analysis on 360 patients from the ASL VCO territory in Italy. Clin Drug Investig. 2014;34(7):513-9.

16. Kubota A, Maeda H, Kanamori A. Efficacy and safety of sitagliptin monotherapy and combination therapy in Japanese type 2 diabetes patients. J Diabetes Investig. 2012;3(6):503-9.

17. Yadav D, Mishra M, Tiwari A, Bisen PS, Goswamy HM, Prasad GB. Prevalence of dyslipidemia and hypertension in Indian type 2 diabetic patients with metabolic syndrome and its clinical significance. Osong Public Health Res Perspect. 2014;5(3):169-75.