Original Article

Safety and efficacy of initial combination of linagliptin and metformin in patients with type 2 diabetes: A subgroup analysis of Indian patients from a randomized, double-blind, placebo-controlled study

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ABSTRACT

Context and Objectives: The number of people with diabetes is increasing exponentially in India. Owing to a unique "Asian Indian Phenotype," Indians develop diabetes a decade earlier and have an earlier onset of complications than Western populations. Therefore, it is essential to evaluate more effective treatment strategies at an earlier stage of disease progression, such as initial combination therapy, in Indian patients. In this study, we evaluated the efficacy and safety of initial combination therapy with linagliptin plus metformin in comparison to linagliptin or metformin monotherapy in Indian patients with type 2 diabetes mellitus. **Methods:** This is a subgroup analysis of Indian patients who participated in a Phase III, 24-week, double-blind, placebo-controlled, trial. Overall, 249 Indian patients were randomized to one of six treatment arms (Two free combination therapy arms: Linagliptin 2.5 mg twice daily [bid] + either low [500 mg, *n* = 36] or high [1000 mg, *n* = 44] dose metformin bid and four monotherapy arms: Linagliptin 5 mg once daily [qd, *n* = 40], metformin 500 mg [*n* = 49] or 1000 mg bid [*n* = 45], or placebo [*n* = 23]). **Results:** The placebo-corrected mean change in glycated hemoglobin from baseline (8.9%) to week 24 was −1.83% for linagliptin + metformin 1000 mg bid; −1.46% for linagliptin + metformin 500 mg bid; −1.30% for metformin 1000 mg bid; −1.00% for metformin 500 mg bid; and −0.77% for linagliptin 5 mg qd. None of the patients in the combination therapy arms had hypoglycemia, whereas there was one event in the metformin 1000 mg bid arm. Rates of adverse event were similar across various treatments. **Conclusions:** In this subgroup analysis of Indian patients, initial combination therapy with linagliptin + metformin was more efficacious in improving glycemic control than the monotherapy arms, with a comparable tolerability profile. The results were comparable to the overall population.

Key words: Dipeptidyl peptidase-4 inhibitor, India, initial combination therapy, linagliptin, metformin, type 2 diabetes mellitus

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.149319

Introduction

Type 2 diabetes mellitus (T2DM) occurs as a result of a progressive insulin secretory defect due to β-cell dysfunction with a background of insulin resistance.[1,2] This condition was originally thought to be a disease of Western countries, but has now become a major global health concern.[3]

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India is infamously termed the "diabetes capital of the world" because of the high prevalence of diabetes in the country.[4] The sixth edition of the International Diabetes Federation Atlas has estimated that India had 65.1 million patients with diabetes in the year 2013. This prevalence is projected to reach nearly 109.0 million by 2035.[5] Indians are characterized by the presence of an "Asian Indian Phenotype" that is associated with an earlier age of onset of diabetes and its complications.[4]

Diabetes has been traditionally managed using a stepwise approach involving the initiation of lifestyle modifications (for example, nutritional interventions and exercise), followed by the addition of oral antidiabetes drugs (OAD) such as metformin monotherapy if the glycated hemoglobin A_{1c} (HbA_{1c}) level remains above the target of 7.0% as recommended by the American Diabetes Association/European Association for the Study of Diabetes guidelines.[6,7] Despite initial monotherapy, majority of patients fail to achieve glycemic goals over time and may require a combination therapy to maintain their HbA_{1c} levels within the target range.[8]

The 2013 American Association of Clinical Endocrinologists guidelines recommends initial combination therapy for patients who present with HbA_{1c} >7.5% or whose glycemic goal is not reached with metformin alone.[8] An optimal initial combination therapy would be one having drugs that have complementary mechanisms of action thereby targeting different core pathophysiologies of T2DM, such as insulin resistance and loss of pancreatic β-cell function.[9] Recent study findings by Williams-Herman *et al*. indicates that initial combination treatment may produce larger improvements in β-cell function when compared with the respective monotherapies.[10] Due to their complementary mechanisms of action, a combination of metformin with a dipeptidyl peptidase (DPP)-4 inhibitor would appear to meet these requirements.[11] Therefore, the aim of our study was to evaluate the efficacy and safety of the new combination of linagliptin and metformin in Indian patients with T2DM.

Linagliptin is a xanthine-based, nonpeptidomimetic, selective DPP-4 inhibitor possessing a unique pharmacological profile compared with other available DPP-4 inhibitors. Following oral administration, majority of linagliptin is eliminated unchanged via the hepatic/biliary route unlike other DPP-4 inhibitors, which are excreted primarily via the renal route. Therefore, linagliptin requires no dosage adjustment in T2DM patients based on their renal or hepatic function.[12] Clinical trials with linagliptin have established its efficacy in terms of decreasing HbA_{1c} levels in T2DM patients while maintaining safety and tolerability profile similar to placebo.[13]

The results of a recent 24-week Phase III study which assessed the initial combination therapy of linagliptin plus metformin showed its superiority over metformin monotherapy in terms of the improvement in glycemic control, with a similar safety and tolerability profile, and no weight gain and a relatively low risk of hypoglycemia.[14] Nearly 30% of patients in this study were from India. Here we report a subgroup analysis of Indian patients.

Materials and Methods

Study design and patient selection

This is a subgroup analysis of Indian patients who participated in a Phase III multicenter, double-blind, randomized, placebo-controlled, parallel-group, international trial of linagliptin plus metformin initial combination therapy in patients with T2DM. The study protocol was approved by the Independent Ethics Committees or Institutional Review Boards of each participating center (Canada, Croatia, Estonia, France, Germany, India, Lithuania, Mexico, Romania, Russia, Sweden, The Netherlands, Tunisia, and Ukraine). In brief, the study comprised a 4-week drug washout period (for patients pretreated with one OAD), followed by a 2-week placebo run-in period (all patients). Subsequently, patients received 24 weeks of double-blind treatment with one of the two combination therapy regimens or four monotherapy regimens. A 1-week follow-up was scheduled after the last clinic visit in all patients who received at least one dose of the study drug [Figure 1]. The participants of the trial were either treatment-naïve or had been treated with not more than one OAD (that was unchanged for the 10 weeks prior to enrolment).

The study was carried out according to the Declaration of Helsinki and Good Clinical Practice (GCP) principles (October 1996) and national GCP regulations where applicable. The protocols and informed consent and patient information forms were reviewed and approved by the local institutional review boards. The inclusion and

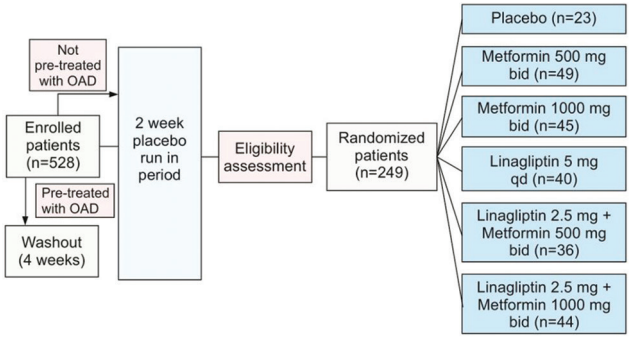

Figure 1: Flowchart of patient disposition

exclusion criteria of study participants have been described elsewhere. Further details on the study design and patient selection are described in the original publication.[14]

Study endpoints and safety measurements

Primary efficacy endpoint

Mean change in glycated hemoglobin levels from baseline to week 24.

Secondary endpoints

Mean change in fasting plasma glucose (FPG) from baseline to week 24 and mean change from baseline in HbA_{1c} and FPG over time.

Safety and tolerability data were collected at screening and throughout the study, and included the incidence of adverse events (AEs), serious AEs and discontinuation due to AEs, 12-lead electrocardiograms, vital signs, and clinical laboratory parameters. Hypoglycemic episodes were recorded and analyzed separately from other AEs, and event intensity was graded according to the investigator's discretion.

Statistical analysis

The efficacy and safety endpoints were summarized using descriptive statistics without statistical tests.

Results

Patient disposition, demographics and clinical characteristics

The data were derived from 791 patients of which 249 patients were enrolled from India. Baseline demographics and clinical characteristics of the study population are presented in Table 1. The mean age of Indian patients was 51.8 ± 10.2 years and 55.0% of the Indian patients were male.

The mean baseline HbA_{1c} value was 8.90% (±1.04 standard deviation [SD]) and the mean FPG value was 183.4 ± 51.3 mg/dL. About 42.6% of patients had been diagnosed with diabetes for <1 year before enrolment and 13.5% had been diagnosed with diabetes for more than 5 years. About 28.3% of patients were on metformin, and 18.1% were on sulfonylureas before enrolment [Table 2]. No patient took more than 1 prior antidiabetes treatment.

Table 1: Baseline demographics and clinical characteristics of the study population

Characteristics	Indian patients
Treated patients, *n* (%)	249 (100.0)
Sex, *n* (%)	
Male	137 (55.0)
Age, mean (SD) (years)	51.8 (10.2)
Weight, mean (SD) (kg)	65.2 (12.1)
BMI, mean (SD) (kg/m^2)	25.72 (3.85)
Height, mean (SD) (cm)	158.9 (8.6)
Waist circumference, mean (SD) (cm)	91.9 (9.4)
Smoking status, *n* (%)	
Never smoked	221 (88.8)
Ex-smoker	14 (5.6)
Currently smokes	14 (5.6)
Alcohol consumption, *n* (%)	
Nondrinker	233 (93.6)
Average consumption	16 (6.4)
Excessive drinker	0
eGFR according to MDRD, (ml/min), *n* (%)	
≥90 (normal renal function)	145 (58.2)
60 - <90 (mild renal impairment)	97 (39.0)
30 - <60 (moderate renal impairment)	4 (1.6)
<30 (severe or endstage renal impairment)	0
Missing	3 (1.2)
eCCR (Cockroft–Gault), (ml/min), *n* (%)	
≥80 (normal renal function)	159 (63.9)
50 - <80 (mild renal impairment)	79 (31.7)
30 - <50 (moderate renal impairment)	8 (3.2)
<30 (severe or end stage renal impairment)	0
Missing	3 (1.2)

eCCR: Estimated creatinine clearance, eGFR: Estimated glomerular filtration rate, MDRD: Modification of diet in renal disease, SD: Standard deviation, BMI: Body mass index

Table 2: Baseline efficacy parameters

Clinical characteristics	Indian patients, *n* (%)
Number of patients	237 (100.0)
Baseline HbA_{1c}, mean (SD), (%)	8.90 (1.04)
<7.0	1 (0.4)
7.0 – <8.0	49 (20.7)
8.0 – 9.0	81 (34.2)
≥9.0	106 (44.7)
Baseline FPG, mean (SD), (mg/dL)	183.4 (51.3)
<126	20 (8.4)
126 – <140	32 (13.5)
140 – <200	106 (44.7)
≥200	79 (33.3)
Missing	0
Duration of diabetes	
≤1 year	101 (42.6)
>1–5 years	104 (43.9)
>5 years	32 (13.5)
Prior antidiabetes treatment at enrolment	
Metformin	67 (28.3)
Sulfonylurea	43 (18.1)

HbA_{1c}: Glycated hemoglobin A_{1c}, FPG: Fasting plasma glucose, SD: Standard deviation

Efficacy: Change in glycated hemoglobin and fasting plasma glucose from baseline

All active treatments lowered HbA_{1c} over time. The combination therapy arms showed a greater decrease in HbA_{1c} compared with the respective monotherapies [Figure 2]. In the metformin monotherapy arms, the higher dose showed a greater decrease in HbA_{1c} than the lower dose. The reduction of HbA_{1c} was most rapid in the first 12 weeks for all active treatments. At week 24, there was an HbA_{1c} fall of 1.6% (±1.16 SD) in the linagliptin 2.5 mg + metformin

1000 mg group, and a rise in HbA_{1c} of 0.23% (±1.42 SD) in the placebo arm, thus providing a mean placebo-corrected reduction in HbA_{1c} was −1.83% [Figure 2].

By 24 weeks, the placebo corrected FPG levels were −33.37 mg/dL with linagliptin + high-dose metformin, −27.01 mg/dL with linagliptin + low-dose metformin, −23.28 mg/dL with high-dose metformin, −18.43 mg/dL with low-dose metformin, and −4.23 mg/dL with linagliptin 5 mg.

Safety and tolerability

The majority of AEs were of mild or moderate intensity across the treatment groups, with no differences observed among the six study arms. The most common AEs for all Indian patients were pyrexia, urinary tract infections, arthralgia, hypertension and back pain [Table 3]. The addition of linagliptin to metformin did not cause an increase in the occurrence of AEs. The occurrence of hypoglycemic events in the free combination therapy arms was shown to be comparable among the groups. The mean exposure to the study drug was about 160 days in Indian patients.

Severe adverse events

One death was reported, because of myocardial infarction, in the metformin 1000 mg bid group, which was assessed as not related to the study medication by the investigator. No fatal events were seen in any of the linagliptin groups. Four Indian patients had nonfatal serious AEs, which were determined as not drug-related by the investigators. There were no significant differences in the occurrence of investigator-defined drug-related AEs among the active treatment groups.

Discussion

Current diabetes management guidelines recommend using combination therapy with metformin in patients who present with an HbA_{1c} >7.5% or who do not reach their target HbA_{1c} with metformin monotherapy.[8] In addition

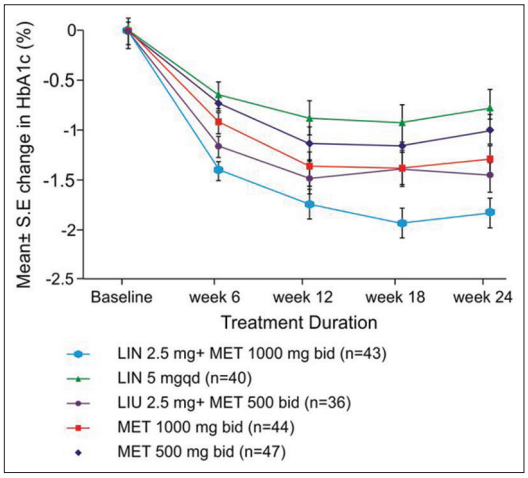

Figure 2: Placebo-corrected mean changes in glycated hemoglobin (HbA_{1c}) from baseline over 24 weeks (full analysis set-last observation carried forward) mean baseline HbA_{1c} values: Placebo = 8.92 ± 1.04%, metformin 500 mg = 8.84 ± 1.02%, metformin 1000 mg = 8.69% ± 0.96%, linagliptin 5 mg = 8.98 ± 1.17%, linagliptin 2.5 mg + metformin 500 mg = 8.96% ± 1.12%, and linagliptin 2.5 mg + metformin 1000 mg = 9.03 ± 0.98%. MET = Metformin, LIN = Linagliptin, HbA_{1c} = Glycated hemoglobin, LOCF = Last observation carried forward, FAS = Full analysis set (all patients in the total set who had a baseline and at least one on-treatment HbA_{1c} value)

Table 3: Adverse event summary for Indian patients

	Placebo	Lina 5 mg	M500 mg bid	M1000 mg bid	Lina 2.5+ M500 mg bid	Lina 2.5+ M1000 mg bid
Patients, *n*	26	43	49	49	37	45
Any AE, *n* (%)	12 (46.2)	20 (46.5)	30 (61.2)	27 (55.1)	20 (54.1)	28 (62.2)
Drug-related AE (investigator defined), *n* (%)	2 (7.7)	4 (9.3)	1 (2.0)	3 (6.1)	4 (10.8)	3 (6.7)
AE leading to discontinuation, *n* (%)	0	1 (2.3)	1 (2.0)	3 (6.1)	2 (5.4)	0
Hypoglycemia, *n* (%)	0	0	0	1 (2.0)	0	0
Gastrointestinal disorders, *n* (%)						
Constipation	1 (3.8)	0	2 (4.1)	0	2 (5.4)	1 (2.2)
Diarrhea	0	1 (2.3)	0	2 (4.1)	1 (2.7)	1 (2.2)
Flatulence	0	0	1 (2.0)	2 (4.1)	0	0
Gastritis	1 (3.8)	1 (2.3)	1 (2.0)	0	2 (5.4)	2 (4.4)
Hyperchlorhydria	0	0	3 (6.1)	1 (2.0)	1 (2.7)	1 (2.2)
Nausea	0	0	0	2 (4.1)	0	0
Vomiting	0	2 (4.7)	0	1 (2.0)	0	0
Pyrexia	2 (7.7)	1 (2.3)	5 (10.2)	2 (4.1)	0	6 (13.3)
Hypertension	1 (3.8)	0	4 (8.2)	1 (2.0)	2 (5.4)	2 (4.4)
Urinary tract infection	0	1 (2.3)	1 (2.0)	0	0	3 (6.7)
Musculoskeletal and connective tissue disorders, *n* (%)						
Arthralgia	0	0	0	1 (2.0)	1 (2.7)	2 (4.4)
Back pain	1 (3.8)	3 (7.0)	0	3 (6.1)	0	2 (4.4)

AE: Adverse event, Lina: Linagliptin, M: Metformin, bid: Twice daily

to the improvements in glycemic control, combination therapy may help reduce pill burden and improve treatment adherence.[8] Initial combination with metformin plus a sulfonylurea is a common therapy in Indian patients. However, this combination suffers from certain drawbacks such as an increased risk of hypoglycemia, weight gain, and potential cardiovascular disease. Furthermore, this initial combination therapy does not appear to be an attractive option because of the possibility of sulfonylureas causing depletion of β-cell insulin stores and induction of β-cell apoptosis.[15] Data from the United Kingdom Prospective Diabetes Study have indicated that intensive treatment of newly diagnosed T2DM patients can lead to long-term benefits including decreased microvascular complications and cardiovascular events.[16]

In this subgroup analysis of Indian patients with T2DM from a randomized Phase III trial, initial combination therapy with linagliptin plus metformin led to a greater improvement in glycemic control than either linagliptin or metformin monotherapy. After 24 weeks of treatment, the mean reduction in HbA_{1c} in the linagliptin 2.5 mg + metformin 1000 mg group was shown to be −1.83% (placebo-corrected value).

The time course and the extent of HbA_{1c} reduction in Indian patients were shown to be similar to that seen in the overall population included in the global trial. In the overall population, the placebo-corrected mean HbA_{1c} changes from baseline at 24 weeks for the different arms were −0.76% for metformin 500 mg, −1.15% for metformin 1000 mg, −0.56% for linagliptin 5 mg, −1.35% for linagliptin 2.5 mg + metformin 500 mg, and −1.7% for linagliptin 2.5 mg + metformin 1000 mg. The change in FPG levels in each arm was also consistent between the Indian subgroup of patients and the overall trial population.[14]

The risk of AEs, especially hypoglycemia, is one of the major concerns associated with combination pharmacotherapy in T2DM. Data from several clinical trials indicate that the linagliptin, either as monotherapy or in combination with other OADs, has good tolerability, with neutral or minimal effects on bodyweight and a very low incidence of hypoglycemia.[2] In the analysis reported here, the majority of AEs were shown to be of a mild or moderate intensity. Discontinuation rates due to AEs were low and similar across the active treatment groups (2.0–6.1%). The main limitation of this analysis is that it is *post-hoc* in nature, and the number of patients per arm is not sufficient to test for a statistical comparison with the overall population.

In addition to the current subgroup analysis, which is from a multicenter, randomized, controlled trial, we found just one other study of initial gliptin plus metformin combination therapy in Indian patients, who were treatment naïve or inadequately controlled on metformin. This single-arm, retrospective, observational analysis conducted by Chatterjee and Chatterjee, in Kolkata, India showed significant HbA_{1c} reduction with the combination of metformin (500 mg) and vildagliptin (50 mg) given once or twice daily (1.4% and 1.9%, respectively) in 280 diabetic patients (average duration of follow-up was 16.8 months).[17]

Conclusion

In this Indian subgroup analysis, which included patients who were treatment naïve and patients who received prior treatment with sulfonylureas or metformin as monotherapy, all active treatments lowered HbA_{1c} and FPG levels over time, with the combination therapies showing greater efficacy than the monotherapies. The addition of linagliptin to metformin was not associated with an increase in AEs, which occurred with low frequency. The results are consistent with those from the overall population included in the global trial.

Acknowledgments

All authors contributed to the study design and analysis of data. The authors are responsible for all content and editorial decisions and were fully involved at all stages of manuscript development. All authors read and approved the final version of the manuscript. We acknowledge BioQuest Solutions Pvt. Ltd for their services in the manuscript writing.

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Cite this article as: Deshmukh V, Sathyanarayana S, Menon S, Patil S, Jones R, Uppal S, *et al*. Safety and efficacy of initial combination of linagliptin and metformin in patients with type 2 diabetes: A subgroup analysis of Indian patients from a randomized, double-blind, placebo-controlled study. Indian J Endocr Metab 2015;19:256-61.

Source of Support: This work was supported by Boehringer Ingelheim, **Conflict of Interest:** None declared.