ORIGINAL RESEARCH

Linagliptin and metformin in Indian patients with type 2 diabetes: Safety and efficacy study

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is a complex condition characterized by various factors. It may be inferred that a therapy strategy focused on addressing a singular fault is improbable to attain normoglycemia or impede the advancement of the disease and therefore there is need of combination therapy. **Objective:** To determine the efficacy and safety of linagliptin in initial combination with metformin in patients with T2DM. **Methods:** This was 1-year randomised, double-blind study in which adults with type 2 diabetes received either metformin 1000 mg bid monotherapy or linagliptin 2.5 mg plus metformin 500 mg bidfor 52 weeks. During the study period mean variation in glycated haemoglobin levels between week 52 and the baseline (primary endpoint) and the average change in fasting blood glucose over time from baseline were measured every 10 weeks. **Results:** Across all patients who received study drug in the extension, the mean age was 57.3 years, and most patients (71.5%) were younger than 65 years. Serum level of HbA1c and fasting glucose were comparable across treatment groups at baseline. HbA1c and plasma glucose decreased in all groups by the end of the 12-month trial however, the reduction was more significant in the combination treatment group than metformin monotherapy. Effect of treatment was not seen on the patients' weight and waist circumference changes, as well as their use of rescue treatment. Safety profile were comparable across the treatment group. **Conclusion:** The combination of linagliptin and metformin over a 12-month period maintained the clinically significant improvements in glycaemic control along with comparable safety profile.

Keywords: Type 2 Diabetes, Metformin monotherapy, Linagliptin plus metformin, glycated haemoglobin

INTRODUCTION

With a history of insulin resistance, β-cell dysfunction leads to a progressive insulin secretory malfunction that eventually results in type 2 diabetes mellitus (T2DM). Though it was formerly believed to be a sickness exclusive to Western nations, this ailment is now a significant worldwide health problem. Due to the high rate of diabetes in the nation, India is notoriously referred to as the "diabetes capital of the world" [1]. According to estimates from the International Diabetes Federation Atlas's sixth edition, 65.1 million people in India had diabetes in 2013. By 2035, it is anticipated that this prevalence would approach 109.0 million [2].

T2DM is a complex condition characterized by various factors, such as reduced insulin secretion by the pancreas, heightened resistance to insulin in peripheral tissues, elevated glucose production by the liver, impaired breakdown of fats, deficiency or resistance to gastrointestinal incretin hormones, excessive glucagon production by α-cells, heightened reabsorption of glucose by the kidneys, and dysfunction of neurotransmitters [3]. It may be inferred that a therapy strategy focused on addressing a singular fault is improbable to attain normoglycemia or impede the advancement of the disease. Before adding oral anti-diabetic medications (OAD) like metformin monotherapy, a progressive strategy to

diabetes management has historically involved starting with dietary changes and increasing physical activity. For most patients, metformin is recommended as the first prescription in addition to lifestyle modifications [4].

Most patients eventually fail to meet their glycemic objectives even with initial monotherapy, and combination medication may be necessary to keep their HbA1c levels within the desired range [5]. The continuous decline in β-cell activity hinders a significant number of persons from attaining or sustaining normal blood glucose levels by metformin monotherapy [6]. As a result, the inclusion of an additional antihyperglycemic drug with a complementary mode of action becomes necessary.

Many patients with type 2 diabetes need combination therapy to achieve target levels of glycaemic control. Dipeptidyl peptidase (DPP)-4 inhibitors have a distinct glucose-lowering mechanism, shown effectiveness, little tendency to produce hypoglycemia, and weight neutrality, making them attractive candidates for combination treatment with metformin [7]. Since linagliptin is the only DPP-4 inhibitor that is mostly eliminated through biliary routes, individuals with any level of liver or renal impairment can use it without needing to change their dosage. Better glycemiccontrol has been achieved with the loose-pill combination (LPC) of linagliptin and metformin than with either medication alone [8]. Linagliptin and metformin are offered as a single-pill combination (SPC) [7], just as other DPP-4 inhibitors.

Compared to people in the West, Indians get diabetes ten years sooner and have problems early. Consequently, it is critical to assess more efficacious treatment approaches in Indian patients at an earlier stage of the illness development, including first combination therapy. In this study, we assessed the safety and effectiveness of linagliptin plus metformin as an initial combination treatment vs linagliptin or metformin monotherapy in patients with type 2 diabetes mellitus from India.

MATERIALS AND METHODS

STUDY POPULATION

This study was conducted at single centre and designed as randomised, double-blind, parallel-group study. From our outpatient department patients with type 2 diabetes were selected to include in the study after obtaining their consent. We included studies of adult humans with type 2 diabetes, non-insulin dependent diabetes mellitus, or adult-onset diabetes. We excluded patients with type 1 diabetes, impaired glucose tolerance, metabolic syndrome, maturity onset diabetes of youth, and gestational diabetes.We also excluded patients with at least one of the following comorbid conditions: ESLD, ESRD, cancer, new onset diabetes after organ transplant, or a recent cardiovascular event within the 3 months prior to study start. Patients with neurological disorders such as dementia, Parkinson's disease, and multiple sclerosis; rheumatoid arthritis, HIV infection were also excluded from the study.

DRUG INTERVENTION AND RANDOMIZATION

Selected patients were assigned to linagliptin 2.5 mg plus metformin 500 mg (both twice daily [bid]) or metformin 1000 mg bid monotherapy group. These patients were treated with assigned medication for 52 weeks.

STUDY OUTCOMES

Primary efficacy endpoint: Mean variation in glycated haemoglobin levels between week 52 and the baseline.

Secondary endpoints: The average change in fasting blood glucose over time from baseline.

Safety and tolerability: Vital signs, 12-lead ECGs, clinical laboratory parameters, incidence of adverse events (AEs), major AEs, and discontinuation owing to AEs were among the information gathered during screening and the course of the trial. Hypoglycemic episodes were evaluated based on the investigator's judgment, and they were documented, examined, and analyzed independently of other adverse events.

STATISTICAL ANALYSIS

Descriptive statistics were used to summarize the safety and effectiveness outcomes without the need for statistical testing.

RESULTS

DEMOGRAPHIC CHARACTERISTICS

Study was conducted in 178 diabetic patients who received either metformin alone (n=71) or Linagliptin 2.5 + metformin 500 (n=107). During the treatment period 3 patients discontinued the study and we collected the data from 175 patients. Across all patients who received study drug in the extension, the mean age was 57.3 years, and most patients (71.5%) were younger than 65 years. More than 60% patients were men (66% in metformin alone group and 66% in combination group.Demographic characteristics and diabetes history were comparable for both the treatment groups (Table 1). Most of the patients had diabetes for 1 to 5 years. Mean HbA1c and fasting blood glucose values were similar between study arms.

Table 1: Baseline characteristics of study subjects

Characteristics	Metformin 1000 (n=70)	Linagliptin 2.5 + metformin 500 (n=105)
Age (years)	57.2 ± 6.7	57.5 ± 7.1
Female (%)	24 (34.3)	35 (33.3)
BMI (kg/m2)	30.1 ± 3.2	29.9 ± 2.9
Duration of type 2 diabetes (%)		
≤ 1 year	23 (32.9)	39 (37.1)
> 1–5 years	27 (38.6)	43 (41.0)
> 5 years	19 (27.1)	23 (21.9)
HbA1c (%)	8.05 ± 1.14	8.11 ± 1.11
Fasting blood glucose(mg/dl)	156.2 ± 17.1	158.7 ± 19.2

Values are mean ± standard deviation or % of patients.

EFFECT OF TREATMENT ON HBA1C AND BLOOD GLUCOSE LEVEL

In the patients receiving either of the treatment, serum level of HbA1c and fasting glucose was evaluated at baseline and every 10 weeks (Figure 1). The mean ± SD HbA1c was comparable across treatment groups at baseline (metformin 1000: 8.05 ± 1.14%; linagliptin 2.5 + metformin 500: 8.11 ± 1.11%, and had decreased in all groups by the end of the 12-month trial (Figure 1A). Mean change in HbA1c was found -0.76 at 10 weeks and it increased upto -1.18 by 52 weeks in metformin 1000 group. In combination the decrease in the HbA1c was significant as compared to in metformin 1000 group (all time points $p<0.001$). Mean change in HbA1c was found -0.96 at 10 weeks and it increased upto -1.98 by 52 weeks in combination group.

Similar effect was noticed in the change in the fasting blood glucose level following drug treatments. The mean ± SD FBG was comparable across treatment groups at baseline (metformin 1000: 156.2 ± 17.1 mg/dl; linagliptin 2.5 + metformin 500: 158.7 ± 19.2mg/dl, and had decreased in all groups by the end of the 12-month trial (Figure 1B). Mean change in FBG was found -10 mg/dl at 10 weeks and it increased upto -18.40 mg/dl by 52 weeks in metformin 1000 group. In combination group, the decrease in the HbA1c was significant as compared to in metformin 1000 group ($p<0.001$ all time points). Mean change in HbA1c was found -18 mg/dl at 10 weeks and it increased upto -26 mg/dl by 52 weeks in the combination group.

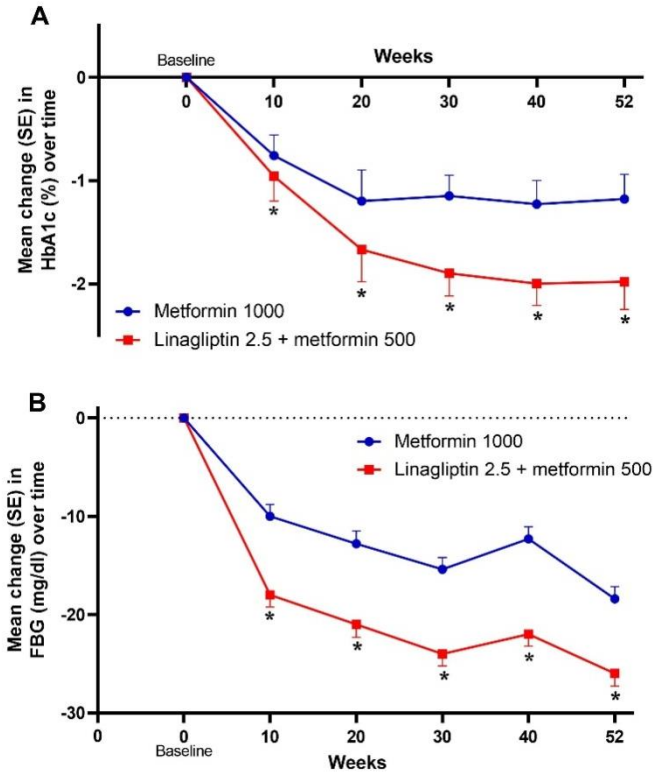

Figure 1: Mean change in glycosylated haemoglobin (HbA1c, A) and fasting blood glucose level in the type 2 patients who received treatment with metformin 1000 or combination of metformin 500 + Linagliptine 2.5 mg/kg.

SECONDARY OUTCOMES

The patients' weight and waist circumference changes, as well as their use of rescue treatment, were examined. Compared to the linagliptin 2.5 + metformin 500 (32.2%) treatment groups, the linagliptin 2.5 + metformin 1000 treatment group had a decreased overall rate of rescue drug usage (17.5%). There were no clinically significant weight changes over the research period. The mean body weight rose by 1.4 ± 0.7 kg in the metformin 1000 group and by 1.2 ± 0.3 kg in the linagliptin 2.5 + metformin 500 group. In a similar vein, there were no statistically significant variations in the groups' changes in waist circumference.

SAFETY

The rates of treatment-emergent adverse events (AEs) in the treated set were similar in all groups over the research period, ranging from 57% to 65%. The majority of adverse events (AEs) were deemed unrelated to the study medication and were of mild to moderate intensity. By desired duration, hyperglycemia and worsening diabetes mellitus were the most common adverse events. Dozens of individuals suffered serious adverse events (SAEs). Patients with pancreatitis or specified cutaneous adverse responses were absent. Hepatic adverse events were rare, and the rates were similar in either group. Renal failure was diagnosed in one patient, and hypersensitivity responses (bronchospasm) in another patient were documented. The metformin 1000 set of patients had both of these occurrences documented.

DISCUSSION

According to current diabetes treatment guidelines, patients who do not achieve their goal HbA1c with metformin alone or who present with a HbA1c >7.5% should use combination therapy with metformin [9]. Combination therapy may help lower pill load and increase treatment adherence in addition to improving glycemic control [9]. For Indian patients, a sulfonylurea combined with metformin is often used as a first combination. Nevertheless, there are a few disadvantages to this combination, including a higher chance of hypoglycemia, weight gain, and maybe cardiovascular disease. Additionally, the potential for sulfonylureas to deplete β-cell insulin reserves and induce β-cell death makes this first combination treatment an unappealing option [10]. Higher HbA1c levels are linked to a higher chance of receiving combination therapy, which may be a reflection of expert groups' recommendations that patients who are unlikely to benefit from monotherapy should instead be evaluated for initial combination therapy (rather than stepwise addition of agents) [11]. Combining metformin with a DPP-4 inhibitor yields better HbA1c control than either monotherapy, and combination treatments give the benefits of early target HbA1c control and target maintenance without the requirement for additional medicines in clinical practice [12]. Additional benefits of using metformin with a DPP-4 inhibitor include the absence of significant safety issues and an increased risk of weight gain or hypoglycemia.

Glycemic control improved more with linagliptin + metformin beginning combination treatment than metformin alone in this clinical study of T2DM patients from India. Following 52 weeks of medication, it was shown that the group receiving linagliptin 2.5 mg plus metformin 1000 mg had a significantly lower mean HbA1c than the group receiving metformin monotherapy. It was demonstrated that the duration and degree of HbA1c decline in Indian patients were comparable to those observed in the international study. It has been demonstrated in the past that linagliptin and metformin initial combination treatment is superior than metformin monotherapy in individuals with type 2 diabetes, with considerably better reductions in HbA1c and fasting blood glucose levels over a 6-month period [13]. Data for a prolonged period of up to 52 weeks were supplied by this study. The total trial population and the Indian subgroup of patients showed consistency in the change in fasting blood glucose levels in each arm [13].

For certain individuals, a progressive approach to therapy may not be recommended over initial combination therapy. Patients with high vs moderate baseline HbA1c values saw the largest HbA1c reductions with combination medication, in keeping with the findings of the first study 7 [13]. All treatment-related and treatment-emergent adverse events (AEs) had similar rates in each research arm. This supports the findings of earlier research showing that linagliptin with metformin is weight neutral over the long run and is linked to a low incidence of hypoglycemia [14].

CONCLUSION

Furthermore, the combination of linagliptin and metformin over a 12-month period maintained the clinically significant improvements in glycaemic control. The results of this one-year comparative effectiveness study support the use of combination therapy for the early treatment of type 2 diabetes because patients with the disease are chronic and will need glucose-lowering combination therapies, such as linagliptin and metformin, for many years.

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