Original Research Paper

Volume - 11 | Issue - 10 | October - 2021 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Diabetology

CLINICAL EFFECTIVENESS OF FIXED DOSE COMBINATION OF EMPAGLIFLOZIN AND LINAGLIPTIN (EMPA/LINA) IN PATIENTS WITH TYPE 2 DIABETES MELLITUS UNWILLING TO CONTINUE BASAL INSULIN THERAPY: A REAL-WORLD EXPERIENCE IN INDIAN SETTING

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ABSTRACT Many T2DM patients are reluctant to continue injectable insulin therapy affecting medication adherence. The objective was to investigate the clinical effectiveness with empagliflozin/linagliptin (EMPA/LINA) combination in patients unwilling to continue insulin therapy. In this retrospective assessment, a total of 60 patients [(41 men, 19 women); age (± S.D.) 53.38 ± 8.49 years and disease duration 5.67±1.89 years; baseline HbA1c: 7.1±0.58%; BMI: 28.25±4.07 kg/m2 were initiated with EMPA/LINA (25/5 mg) after thorough assessment. During 12-week period, there was modest improvements in glycemic profile [baseline vs. endpoint; HbA1c: 7.1±0.58% versus 7.1±0.55% (p < 0.63), FPG 129±14 mg/dl versus 125±9.3 mg/dl, PPG 154±18 mg/dl versus 143±11 mg/dl (p=0.01), proportion of patients achieving A1C goal with no major hypoglycemia was improved from 37% to 81.48%. The incidence of overall hypoglycemia was reduced. These findings suggest that patients with stable glycemic status reluctant to continue insulin may have effective transition to EMPA/LINA therapy.

KEYWORDS : empagliflozin and linagliptin, type 2 diabetes, Insulin, Hypoglycemia

INTRODUCTION

Though initially patients with type 2 diabetes (T2D) are treated with oral hypoglycemic agents (OHA), its chronic, progressive nature necessitates employing the insulin therapy in patients.[1] The Centres for Disease Control and Prevention National Diabetes Statistics Report found that 2.9 million people with diabetes (14%) use insulin only and 3.1 million (14.7%) use a combination of insulin and OHAs.[2,3] In India, according to the estimates by Mohan et al., four out of ten patients are being treated with insulin either alone or in combination with OHA.[4] The major concern with success of insulin therapy is the level of adherence. Cramer et al., in the systematic review reported an adherence rate only between 62 to 64% to insulin in patients with T2D.[5] A large-scale study in more than 1400 T2D patients suggested that insulin omission or non-adherence is frequent especially in younger, male, patients.[6,7] Also, patients facing more logistical barriers, concerned that insulin treatment required lifestyle changes, continuous monitoring or were disappointed with the flexibility of injection timing were particularly non-adherent.[7,8] Further the increase in body weight, predominantly adipose tissue associated with insulin therapy (~3-9 kg) also offsets the potential benefits by adversely affecting diabetic and cardiovascular morbidity and mortality.[9] Further clinical inertia and disinclination around insulin use continues at least in part also because of apprehensions around hypoglycemia.[8] Patients' anxiety about hypoglycemia tend to increase their caloric intake. Additionally, reduced glycosuria, catch-up weight, and neural effects on appetite regulation could be the other mechanisms of insulin-associated weight gain. Management of obese T2D patients on insulin therapy due to recurrent weight gain and worsening of glycemic control is therefore more exigent.[9] Previous studies have demonstrated that the addition of SGLT2 inhibitors or DPP-4 inhibitors to background insulin therapy can offer several clinical benefits and, may reduce the incidence of insulin-associated side effects mainly weight gain and hypoglycemia.[8,10] Hence, in patients who discontinued insulin due to some reasons and switched to empagliflozin/linagliptin we sought to determine whether the optimum glycemic control was maintained without patient related adverse effects weight gain or hypoglycemia.

METHODS

This was a 12-week, retrospective, observational study in 60 patients diagnosed with T2D with HbA1c < 7.5% aged ≥18 years of age who were on stable basal insulin for more than 3 months period. It was carried out in accordance with the principles of the Declaration of Helsinki revised in 2008. Individuals included in the study cohort attending the endocrine department of a super-specialty hospital in Eastern India from January 2019 to August 2019 expressed their wish to discontinue the insulin therapy due to various reasons such as associated weight gain, inconvenience of injectable formulation, restriction in lifestyle, especially in younger or active individuals. (Figure 1). Exclusion criteria were type 1 diabetes or past history of ketoacidosis, hypersensitivity reaction to empagliflozin or linagliptin; history of chronic pancreatitis or pancreatectomy; history of repeated episodes of unexplained hypoglycemia, C-peptide <□ 0.2□ pmol / L; anti-glutamic acid decarboxylase (GAD) or anti-islet antibodies; poorly controlled diabetes, fatal disease, heart failure and significant kidney or liver disease, experiencing infection or planning to have surgery, pregnancy or breast feeding.

The patients who were switched from basal insulin therapy to once daily oral EMPA/LINA (25/5 mg) following 48-hour washout period were included in the analysis considering no signs of insulinopenia, as an add-on to coexisting therapy with metformin, sulfonylurea, pioglitazone and/or a-glucosidase inhibitor pharmacotherapy for at least 12 weeks follow-up period. These data were retrieved from the electronic database of a hospital in Kolkata, India; the data was organised and then analysed. Two subjects discontinued therapy after the switch out of the 60 patients enrolled. The participant developed a subconjunctival haemorrhage within 4 weeks after the switch and had returned to insulin therapy; the second case lost the optimum glycemic control within 2 weeks of therapy after the switch so shifted back to insulin therapy.

Data were processed in Excel-sheet and analysed using the SPSS software. Quantitative variables were summarized using mean and standard deviation. Student's *t*-test or dependent sample t-test was used for testing the significance of differences between the mean values of two continuous variables. The probability (p) level of less than 0.05 was considered significant.

RESULTS

The baseline demographics and characteristics in this observational study are shown in **Table 1**.

Characteristics	ObservationsinStudy Participants
N	60
Age(years)	53.38±8.49
Sex(Male%)	68%
Weight(inkg)	72.85±10.19
BMI(kg/m^2)	28.25±4.07
DurationofT2Dinyears	5.67±1.89
ConcomitantComorbidities	
• Hypertensionn(%)	16(27)
• Dyslipidaemian(%)	7(11)

• Hypertension+Dyslipidaemian(%)	7(11)
Co-medication	
• Dualtherapy(%,N)	16(27)
• Tripletherapy(%,N)	44(73)
TypesofBasalinsulin(%,N)	
• NPH	19(32)
• Glargine	22(37)
• Detemir	18(30)
TDD(IU)	13.95±2.8
TDD(IU/kg)	0.17±0.02
Durationofinsulin(months)	6.0±3.1
BaselineHbA1c%	7.1±0.58
BaselineFPG(mg/dl)	128.51±13.77
BaselinePPBG(mg/dl)	153.93±17.73

Table 1. Baseline Demographics And Characteristics

N: number of patients; BMI: Body mass index; T2D: type 2 diabetes; IU: international units; NPH: Neutral Protamine Hagedorn; TDD: Total daily dose; HbA1c: glycated haemoglobin; FPG: Fasting plasma glucose; PPG post-prandial glucose

Among the patients who wished to cease insulin treatment, 56 patients cited reasons for their choice. Primarily the injection related difficulties were one of the reasons for discontinuation, followed by absence of support, weight gain and occurrence of hypoglycemia or fear of hypoglycemia. **Fig 1**

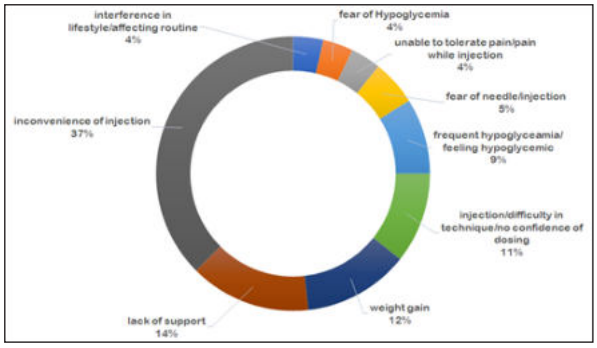

Figure 1. Reasons For Discontinuation Of Insulin In T2D Patients (%)

At the end of 12 weeks, the glycemic parameters namely HbA1c and FPG were maintained even after the switch from insulin to EMPA/LINA. **Table 2.**

Parameters	Baseline (N=60)	Follow up after 12 weeks (N=58)	Change	p value
HbA1c (%)	7.1±0.58	7.1±0.55	-0.06±1.01	0.63
FPG (mg/dl)	129±14	125±9.3	-3.67±13.37	0.13
PPG (mg/dl)	154±18	143±11	-10.92±13.65	0.0001
Body weight	72.85±1 0.19	70±9.9	-2.1±1.71	0.16
Patients achieved target Hba1c (%) n	40 (24)	45 (27)	+5	0.71
Patient with at least one episode of hypoglycemia % (n)	61.7 (37)	20 (12)	-41.7	<0.0001
Patients achieved target Hba1c without occurrence of hypoglycemia % (n)	37 (9)	81.48 (22)	-44.48	0.0018

Table 2. Effect Of EMPA/LINA (25/5 MG) On Glycaemic Parameters Of Individuals With Diabetes

Data are expressed as mean ± standard deviation or as number and percentage. FPG: Fasting plasma glucose; PPG post-prandial glucose; Hba1c: glycated haemoglobin; EMPA/LINA: empagliflozin/ linagliptin.

Patients continued to nearly achieve the target HbA1c <7% recommended by American Diabetes Association 2021 standard of care (ADA 2021). HbA1c was maintained around 7.1% at 3 months after the switch in patients who completed the planned 3-month study. There was non-significant decrease in the change in mean FPG level. However, the decrease in PPG level was observed to be significant (P< 0.01) compared to the PPG at baseline viz., prior to switching to EMPA/LINA. **Table 2**

The Interestingly, patients achieving the target HbA1c without occurrence of significant hypoglycemia was greater after initiation of EMPA/ LINA therapy. The mean body weight was reduced by 2.1 (±1.71) kg, but the decrease was not statistically significant and thereby BMI did not show a significant change.

Over a month period prior to the commencement of EMPA/LINA therapy, treatment with insulin regimen was associated with 43 episodes of hypoglycemia in 37 (61.66%) patients. However, across three months of treatment, only 12 episodes of hypoglycemia viz., mild to moderate in nature (20%) is occurred, mostly associated with sulfonylurea therapy in background. The records did not indicate any severe type of hypoglycemic episodes that required hospitalization, or ketoacidosis or any other serious adverse events.

DISCUSSION

Suboptimal adherence to daily insulin injectable therapy is commonly observed among T2D patients and attributed to various physician- and patients-related perception despite the fact that treatment is considered as one of the most effective glucose lowering treatment strategy in those patients. Previous reports demonstrate that poor adherence to medications is apparently a major contributing factor of inadequate glycemic control leading to poor quality of life in patients.[11]The patient cohort in the present study who were keen to discontinue the injectable insulin therapy are relatively younger with short duration of diabetes which is in accordance with earlier questionnaire based survey reports [12] and International Diabetes Management Practices Study (IDMPS). These were predominantly due to challenges associated with the negative perception about the injectable form.[13] Among several others, occurrence and fear of hypoglycemia together were the major basis for declining continuation of treatment with insulin along with weight gain.

The current American Association of Clinical Endocrinologists (AACE)/European Association for the Study of Diabetes (EASD) and American Diabetes Association (ADA) guidelines suggest a goal A1C of 6.5% and 7%, respectively.[14] The T2D patients in this retrospective, observational study who were switched to EMPA/LINA had a mean baseline HbA1c of 7.1%, the switch was therefore considered suitable after adequate assessment of appropriate patients related factors. [12] Replacement of insulin with EMPA/LINA (25/5mg) resulted in preservation of the glycemic status with no further significant change in HbA1c and FBG in these patients with previously well-controlled hyperglycemia on insulin with dual or triple combination of agents belonging to either class of OHAs namely metformin, SU, DPP-4 inhibitors, a-glucosidase inhibitor. Several previous randomized studies which evaluated EMPA/LINA as an add-on to metformin found significant improvements in HbA1c (-1.19%).[15] Nevertheless, the decrease in PPG was significant compared to the baseline values. As also shown in the study by Forst et al (2017), in patients who failed on metformin, sequential addition of the mono-components of this combination showed additive effects on PP glucose control due to their potential complementary effects. The effects were proposed to be associated with a significant reduction in postprandial insulin levels, an improvement in the conversion rate of proinsulin and marked reduction in postprandial glucagon concentrations. [16] The authors proposed that the lower postprandial insulin levels during treatment with empagliflozin could be due to the glucosuric effects of the drug and diminished insulin requirement due to reduced postprandial glucose peaks. Linagliptin has shown to improve the PPG control via decrease in the glucagon / insulin ratio, thus offsetting the effect of Empagliflozin on endogenous glucagon level. [14] DPP-4 inhibitors result in higher levels of active incretins which stimulate the release of insulin, thus improving glycemic control. [17] The aggregate effects on PPG control, perhaps is facilitated by complementing effects of EMPA/LINA on α - and β - cell functions.[14]

Recently a qualitative, prospective study comparing biphasic insulin with metformin and triple oral hypoglycemic agents (OHA) found that the mean body weight increased by 4.48 kg in insulin/metformin and decreased by 0.46 kg in triple OHA at the end of 12-weeks. [18] Rosenstock et al, when compared insulin only to insulin/Empa treatment, an increase in weight was observed with insulin only group

whereas continued weight loss was observed in the insulin/ empagliflozin group. This was attributed to the urinary glucose excretion and mild osmotic diuresis.[19] Meta-analysis of several studies in which Empagliflozin (10 and 25 mg) as an add-on to Metformin was compared to other add-on treatments has demonstrated significant (<0.00001 and 0.0002) benefit in terms of reduction of body weight.[20] Linagliptin is known to be weight-neutral.[21,22]

In T2D patients on insulin, major challenge of controlling weight gain is crucial. The distress of weight gain with some medications also contributes to psychological insulin resistance.[23, 24] With insulin therapy, a 1% decrease in HbA1c level is accompanied with a 2-kg weight gain over a year.[25] In the current study which included overweight patients (mean BMI 28.39 kg/m^2), the HbA1C remained fairly near target levels with EMPA/LINA yet reducing weight by approximately 2 kg in 12 weeks. Though not statistically significant, this effect on body weight could be particularly important in T2D patients who are overweight or obese and therefore were inclined to discontinue or become non-compliant to diabetes pharmacotherapy, especially insulin, which may have led to poor glycemic control.[26]

The use of insulin in patients with T2DM is associated with a high risk of hypoglycemic events, thwarting the management of hyperglycemia. Fear and incidences of hypoglycemia reduce adherence to medication.[27] In the current study, it was found that the incidence of hypoglycemia were reduced by more than three times after switching from insulin to EMPA/LINA. However, the records did not document any episodes of hypoglycemia or ketoacidosis which required hospitalization. Also, the EMPA-REG MDI and BASAL 52- and 78-week trials respectively, showed that in patients with T2D inadequately controlled on insulin doses, empagliflozin improved glycemic control without increasing the risk of hypoglycemia.[18,25] It has been suggested that the low risk of hypoglycemia in patients with Empagliflozin is attributed to its insulin-independent mechanism; the partial inhibition of renal glucose reabsorption, a moderated effect of SGLT2 inhibition at low glucose levels due to physiological decline in glomerular filtration rate; a reciprocal balancing increase in gluconeogenesis in the liver.[25] DPP-4 inhibitors too have the advantage of no increased risk of hypoglycemia since they enhance insulin secretion in a glucose-dependent manner, thus preventing hypoglycemia either when used as monotherapy or in combination with certain antidiabetic agents including insulin.[20,21,28] T2D patients even when well-controlled on insulin are inclined to prefer OHAs, which could be at least in part be due to the perception that their illness is less serious when on oral agents[29] apart from the other reasons listed earlier.

A physician and patient will deliberate on timely transition from insulin therapy to safe and efficient OHA only when there has been appropriate assessment of clinical status of the patient weighing the benefit risk associated with treatment modality. The results of present retrospective study, though in a small number of patients with stable glycemic status, continued to exhibit optimum glycemic status maintained successfully even after cessation insulin therapy. Additionally, the incidence of hypoglycemia was significantly reduced along with avoidance of the various negative aspects of a medication which required regular, daily use injectable with precise. Hence, it suggests that patients with stable glycemic status reluctant to continue insulin, could be switched to a combination of EMPA/LINA (25/5 mg) along with other concurrent OHAs. However, these findings should be verified in well-controlled, prospective long term studies with an adequate sample size to derive the confirmatory reports.

Certain limitations need to be acknowledged while interpreting the result. The retrospective nature and source of study population from a tertiary institute may have introduced selection bias. Lesser number of cases in cohort are more likely to affect the alfa power of analysis and may have an impact on final estimate. Also, we were limited to the information available in reference notes, which occasionally were inconsistent or absent.

To conclude, the transition from insulin therapy to oral glucose-lowering treatment like EMPA/LINA combination results in maintaining the preserved glycaemic status without increased risk of hypoglycaemia. These findings suggest that patients with stable glycaemic status reluctant to continue insulin could be switched effectively to a novel combination of EMPA/LINA along with other OHAs.

Conflict of interest: There is no conflict interest.

Acknowledgments: No

Source of funding: Nil

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