ORIGINAL RESEARCH ARTICLE

Efficacy and Safety of Addition of Empagliflozin in Diabetic Patients Uncontrolled with Triple Therapy-Glimepride/ Metformin and Sitagliptin

S R Pattanaik[1], Padala Ravi Kumar[2]

[1]Associate Professor, Department of Endocrinology, MKCG Medical College, Berhampur, Odisha, [2]Assistant Professor, Department of Endocrinology, MKCG Medical College, Berhampur, Odisha, India

Corresponding author: Dr Padala Ravi Kumar, Assistant Professor, Department of Endocrinology, MKCG Medical College, Berhampur, Odisha, India

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ABSTRACT

Introduction: The aim of the study was to examine the efficacy and safety of empagliflozin as add on therapy in type 2 diabetes patients inadequately controlled on triple drug therapy with glimepiride, metformin and sitagliptin.

Material and methods: This prospective observational study conducted in a clinical setting included subjects with T2DM aged between 40-70years with inadequate disease control on triple combination therapy glimepiride(8mg), metformin(2gm) and sitagliptin(100mg) and had HbA1c>7.5%. Patients with CKD, MI, severe sepsis and overtly osmotic symptoms were excluded. In all the cases baseline clinical and anthropometry was taken. Empagliflozin 25mg was added to these patients for 12 weeks and the change in HbA1c and renal parameters noted after 3months and change in fasting and postprandial plasma glucose every month was observed for 3months. Any adverse events during the course of the study was duly noted. The pre and post therapy anthropometry and biochemical parameters were analyzed using paired t-test and Wilcoxon signed rank test.

Results: The study included 40 T2DM patients with mean age and duration of diabetes respectively 54±4.2yrs and 6.1±2.26yrs respectively. FPG, PPG, HbA1C, body weight showed significant reduction following add-on treatment with empagliflozin 25mg to triple therapy with glimepiride, metformin and sitagliptin ($p<0.001$). mean change in HbA1c after 12 weeks of empagliflozin 25mg was -0.67%. HbA1c decrease of ≤0.7% and >0.7% observed in 27(67.5%) and 13 (22.5%) of patients. Adverse events included genital mycotic infections and UTI.

Conclusion: Empagliflozin treatment as an add-on therapy to triple drug treatment with metformin, glimepride and sitagliptin in adequately controlled T2DM patients is a safe option in selected patients.

Keywords: T2DM, Empagliflozin, Triple Therapy

INTRODUCTION

Diabetes mellitus is one of the significant health problems in the world associated with high morbidity and mortality and the incidence is increasing in geometric proportion around the world. The International Diabetes Federation predicted that the by 2045, nearly 700 million people will be affected by this malady around the world.it has been estimated that 77 million adults are affected with diabetes in India.[1] T2DM is responsible for 90-95% cases and is responsible for 5million deaths per year.[2]

Treatment for diabetes is usually initiated with monotherapy usually with metformin or as combination therapy with different agents either as double or triple drug combination.[3,4] Triple drug combination therapy was observed to be associated with significant reduction in HbA1c in different studies.[5] However there are no guidelines or recommendations how to control glycaemia in people who fail triple drug therapy other than introducing insulin.[6] Hence there has always been a place for newer therapeutic agents. SGLT2 inhibitors were introduced in the early part of this decade for this purpose.[7] These drugs prevent reabsorption of glucose from proximal convoluted tubules there by reducing hyperglycemia.[8] These agents work in parallel with blood glucose concentration thereby decreasing hypoglycemia without stimulating the beta cells.[8]

Empagliflizon is a member of this class of drugs which was approved by US FDA in 2014. The EMPA REG trial in 2015 has shown that Empagliflozin has many pleiotropic beneficial effects besides glycemic control. These include blood pressure lowering, weight loss, cardiovascular and renal benefits besides overall mortality benefit.[9] Efficacy and safety of this drug is well established as monotherapy.[10] However literature evidence of safety and efficacy after quadruple drug combination therapy is limited. Present study was conducted to evaluate the efficacy and safety addition of empagliflozin 25mg/day to T2DM patients who were inadequately controlled with glimepiride/metformin and sitagliptin.

MATERIALS AND METHODS

This prospective observational study was carried out in the diabetes clinic of MKCG Medical College from April 2019 till August 2019. Informed consent from all the subjects was taken prior to inclusion in the present study. The study participants included T2DM patients aged 40-70yrs who had uncontrolled glycemia (HbA1c>7.5%) on glimepiride (6-8mg/d), Metformin (2gm/d) and sitagliptin (100mg/d). Patients who had overt osmotic symptoms, history of MI, CVA, CKD,, severe sepsis were excluded from the study. Demographic and clinical characteristics like age, sex, height, weight, duration of diabetes and any complications were obtained from all the patients. All patients were treated with empagliflozin 25mg/d along with triple drug treatment with glimepiride upto 8mg/d, metformin 2gm/d and sitagliptin 100mg/d for 12 weeks. Body weight, blood pressure, fasting plasma glucose, postprandial plasma glucose, HbA1c were measured before and after therapy. Any adverse events during the course of the study was recorded.

STATISTICAL ANALYSIS

Comparison of pre and post therapy anthropometry and laboratory parameters were performed by paired t- test for normal data and Wilcoxon signed rank test for data without normal distribution. P value<o.o5 was considered statistically significant. Percent reduction in HbA!c of ≤0.7% and >0.7% were verified as prespecified end points. All the statistical analysis were performed using SPSS14.

RESULTS

The study included 48 T2DM patients, out of which 8 dropped out because of withdrawal of consent or opting for insulin. Forty patients completed the study. The mean age of the patients was 54±4.2yrs and duration of the diabetes was 6.12yrs±2.2yrs. The male female ratio was 1.5:1. The demographic and anthropometric data are shown in Table 1. Comparison of variables before and after treatment with empagliflozin 25mg/d for 12weeks showed that the body weight, FPG, PPPG and HbA1c significantly decreased (p<0.001). However renal parameters did not change significantly. (Table 2). The mean decrease in body weight was 1.71±0.5kg and SBP and DBP was -3.7 and -2.6mmHg respectively. Body weight decreased in 23 subjects, increased in 7 and remained stable in 10 patients. Systolic blood pressure decrease in 26 patients and increased in 1 patient and remain unchanged in 13 patients. Diastolic blood pressure decreased in 30 patients and remain unchanged in rest. Percent reduction in prespecified HbA1c cut-off showed 27 (67.5%) patients had decrease of HbA1c ≤0.7% and 13 (22.5%) patients achieved a decrease of >0.7% HbA1c.

There was no dropout due to adverse reactions such as serious deterioration of renal function, complications due to osmotic diuresis, DKA and amputation. Adverse reactions noted were mild, UTI 8% in males and 18% in female and mycotic infections 14% in males and 20% in females.

DISCUSSION

The present study showed that T2DM patients uncontrolled with maximal doses of glimepiride, metformin and sitagliptin still showed significant reduction in HbA1c, FPG, PPG, body weight, SBP and DBP after 12weeks of therapy with 25mg of empagliflozin.

SGLT2 inhibitors inhibits reabsorption of filtered glucose at the level of proximal convoluted tubule in the kidney with excretion of glucose in the urine.[11] Moreover this insulin independent mechanism results in substantially less risk of hypoglycemia.[12] The results of present study in line with observation by Neelard and colleagues.[13] Devi et al (2017) in a met analysis of randomized control trials have substantiated the safety and efficacy of empagliflozin as monotherapy as well as add on therapy to other agents.[10] Even in patients with CKD, empagliflozin reduces HbA1c as demonstrated by Barnett and associates.[13]

On the other hand treatment with empagliflozin confers several non-glycemic benefits such as reduction in blood pressure and body weight.[10] Similar observations are also observed in present study where 23 patients showed significant reduction in bodyweight. The reduction body

Age (yrs)	54±4.2yrs
Male: female	24:16
Duration of diabetes(yrs)	6.12±2.26
BMI kg/m2	26±1.2
Hypertension BP≥140/or 90mmHg(=N)	15

Table-1: Demgraphic and Anthropometry of study patients

	Base line	1month	2month	3month	p
Body weight kg	63.65±5.01			61.94±5.1	<0.001
SBP mmHg	147±3.1			143.3±2.8	0.01
DBP mmHg	88±2.4			85.4±1.2	0.01
Urea mg/dl	24.5±4			24±5.6	0.14
Creatinine	0.98±0.16			0.9±0.4	0.17
FPG mg/dl	160±18.4	136±46.5	116±36.4	94.3±30.1	<0.001
PPG mg/dl	302±40.0	230±36.2	170.8±40.4	160±20.1	,<0.001
HbA1c%	7.69±0.53			7.02±0.68	<0.001

Table-2: Comparison of variables before and after Empagliflozin add-on

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weight is believed to be due to loss of calories 240-400kcal/d due to loss of glucose in urine.[6]

Ferranini and colleagues while studying the long-term safety and efficacy of triple combination therapy empagliflozin, metformin and sitagliptin observed significant long-term and short-term safety with this combination.[14] Safety factor was also noted by Shiba et al while studying the effect of empagliflazon in Japanese patient when they reported that the drug to be well tolerated with no case of hypoglycemia requiring assistance.[15] Kohler et al in analyzing pool data from 14 clinical studies noted 0.2% and 0.3% incidence of UTI with 10mg and 25mg empagliflozin respectively compared to 0.4% in placebo group. However they noted 4.7 and5% incidence of mycotic infection with 10mg and 25mg empagliflozin respectively compared to 1.3% in the placebo group.[16] The risk of hypoglycemia was observed to be increased in those with background insulin or sulfonylureas but not with empagliflozin montherapy. The incidence of malignancy, fracture, hepatic injury, venous thromboembolic events, impaired renal events and DKA was similar across the treatment group.[17] Addition of empagliflazone in patiens who were inadequately controlled with metformin and linagliptin over 24 weeks showed significant decrease in HbA1c of 0.7%.[17]

Ridder Straile et al while comparing the effect of addition of empagliflozin or glimepride as add on to metformin have shown better control with empagliflozin compared to glimepride (0.73% Vs 0.66%) over 52weeks. Body weight was significantly reduced with empagliflozin while it was increases with glimepride.[18] In another study HbA1c reduction with empagliflozin and linagliptin combination was better than compared to linagliptin alone.[19]

A search of literature did not reveal any quadruple combination therapy using empagliflozin, glimepiride2, metformin and sitagliptin. Even in uncontrolled T2DM patients on triple therapy addition of empagliflazon appear to be beneficial.

CONCLUSION

In conclusion, empagliflozin may be an excellent add on in T2DM patients who are inadequately controlled with triple drug combination of glimepride, metformin and sitagliptin.

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