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Research Article

Variation in Glycemic and Extra Glycemic Parameters with Initiation of Remogliflozin Etabonate in Patients of T2DM Having a Good Glycemic Control with other SGLT2 Inhibitors

Sanjay Sud[1], Sumit Bhushan[2*], Sachin Suryawanshi[2], Abhishek Mane[2], Sheldon Creado[2], Hanmant Barkate[2]

[1]Diabetology, Doctor Sud's Clinic, Serampore, Hooghly, India

[2]Global Medical Affairs, Glenmark Pharmaceuticals Limited, Mumbai, Maharashtra, India

[*]**Corresponding Author:** Sumit Bhushan, Global Medical Affairs, Glenmark Pharmaceuticals Limited, Mumbai, Maharashtra, India

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Abstract

Introduction: Remogliflozin etabonate is the latest addition to the Sodium glucose co-transporter-2 (SGLT2) inhibitor class of drugs which is a potent and selective inhibitor of SGLT2. A real world non-randomized, single centre, retrospective study was done to assess changes in glycemic and extra glycemic parameters of type 2 diabetes mellitus (T2DM) patients who were well controlled (HbA1c ≤ 7%) with other SGLT2 inhibitors (Dapagliflozin and Empagliflozin), but had difficulty to afford the high cost of therapy from out of pocket expenditure and voluntarily requested for a switchover for economic reasons.

Materials and methods: Retrospective observation of the variations in glycemic and extra glycemic parameters including blood pressure, body weight, lipid profile and eGFR of 32 patients was recorded, when they were initiated on Remogliflozin etabonate, replacing other SGLT2 inhibitors (19 were on Empagliflozin and 13 were on Dapagliflozin). The data was tabulated for a total of three visits (First - initial, Second – at three months from initial and Third- at six months from initial), after which analysis was done.

Results: There were no significant changes in HbA1c value from baseline after initiation of remogliflozin etabonate from dapagliflozin and empagliflozin. There was also no significant reduction of blood pressure, body weight and eGFR from baseline for patients switched from Dapagliflozin. However, the change in blood pressure and body weight was statistically significant for patients switched from Empagliflozin ($p<0.01$).

Conclusion: Remogliflozin etabonate given as 100 mg twice daily is non-inferior to Empagliflozin 10 mg / Dapagliflozin 10 mg given as once daily to patients of T2DM as far as their glycemic goals are concerned with favourable extra glycemic benefit and cost burden reduction of more than 50%.

Keywords: Blood pressure; Diabetes mellitus; HbA1c; Remogliflozin etabonate; SGLT2 inhibitors

Introduction

Diabetes mellitus presents a major health challenge worldwide and a potential economic burden in low-and-middle-income countries like India [1]. According to the International Diabetes Federation report, the prevalence of diabetes in 20–79 years olds in 2021 was estimated to be 10.5% globally (536.6 million people), surging to 12.2% (783.2 million) in 2045. Middle-income countries are expected to experience a greater relative rise in the prevalence of diabetes (21.1%) as compared to high- (12.2%) and low-income (11.9%) countries [2,3]. The incidence of diabetes in India is primarily driven by rising age, dietary transitions, rapid urbanisation, sedentary lifestyle and lack of physical activity leading to obesity [4] Various studies highlighted the financial load posed by diabetes on individuals/households, according to which the average expenses per person per month (pppm) of individuals with diabetes was estimated to be (Rs. 1,357.65 pppm) in India. The total cost of illness for diabetic care without any complications was Rs. 22,456 per patient per annum and with complication was Rs. 30,634 [5].

Type 2 diabetes is a complex metabolic disease which consists of an array of dysfunctions characterized by hyperglycemia that can lead to the development of microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular complications. Glycaemic control has been shown to effectively reduce the incidence and worsening of microvascular complications that lead to increased risk of cardiovascular diseases [6,7]. Numerous clinical trials have provided strong evidence on the efficacy of GLP-1 receptor agonists and SGLT2 inhibitors for lowering cardiovascular and renal risk in patients predisposed to these complications [8]. Updated guidelines from the American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD), and European Society of Cardiology (ESC) in 2019 recommended SGLT2 inhibitors in type 2 diabetes patients for management of such patients [9].

Remogliflozin etabonate (RE) is the latest addition to the SGLT2 inhibitor class of drugs which is a potent and selective inhibitor of SGLT2. It is an orally bioavailable prodrug of Remogliflozin whose clinical profile was found to be a potent, safe and non-inferior agent to the currently available SGLT2 inhibitors. This drug has been priced at a substantially lower cost as compared with other SGLT-2 inhibitors, making it affordable in developing countries like India [10,11]. A real world non-randomized single center retrospective study was done to assess changes in glycemic and extra glycemic parameters of T2DM patients who were well controlled (HbA1c ≤ 7%) with other SGLT2 inhibitors (Dapagliflozin and Empagliflozin), but had difficulty to afford the high cost of therapy from out of pocket expenditure and voluntarily requested for a switchover for economic reasons.

Material and Methods

This was a real world non-randomized single center retrospective study in which 40 patients initiated on Remogliflozin were included, out of which 32 patients completed the two follow ups, (first at three months and second at six months from the date of inclusion). The study was conducted after taking ethical clearance from institutional ethics committee. The variations in glycemic and extra glycemic parameters (blood pressure, body weight, lipid profile and eGFR) were recorded when they were initiated on Remogliflozin etabonate, replacing the other SGLT2 inhibitors they were consuming namely – Dapagliflozin and Empagliflozin.

The inclusion criteria was

- Non-pregnant adults (18 – 60 years)
- T2DM duration ≥ 2 years (as per ADA criteria)
- On oral anti-hyperglycemic agents which included Metformin + Dapagliflozin / Empagliflozin (being taken for ≥ 6 months) with or without other oral agents
- Having HbA1c ≤ 7%
- Blood pressure ≤ 130/80 mm of Hg
- eGFR ≥ 60 ml/min/1.73m^2 (CKD-EPI)
- Normal lipid profile (as per ADA criteria)
- Voluntary declaration for switching over to Remogliflozin etabonate from other SGLT2 inhibitor being consumed due to cost burden

Patients above 60 years, those who were on insulin or suffering from any critical illness like, cancer, recent myocardial infarction, recent recovery from septicemia, recently undergone a major surgery, etc. were excluded from the study. Informed consent was obtained from the patients selected on the basis of the abovementioned inclusion criteria. A washout period of three days was given after discontinuing the SGLT2 inhibitor being currently consumed (Dapagliflozin 10 mg OD / Empagliflozin 10 mg OD), before initiating Remogliflozin etabonate 100 mg BD. The data of 32 patients was tabulated and the retrospective analysis was done.

Results

A total of 32 eligible patient's data was analyzed in this study. The mean age at diagnosis was 45.88 ±6.35 years, with male predominance (62.5%).

The glycemic and extraglycemic parameters of 32 patients (19 were on Empagliflozin and 13 were on Dapagliflozin) are shown in the following table for a total of three visits (First - initial,

Second – at three months and Third at six months from initial). There were no significant changes in HbA1c, blood pressure, body weight and eGFR values from baseline for patients switched from Dapagliflozin (Table 1). This was statistically significant for patients switched from Empagliflozin ($p<0.01$) (Table 2)

Lipid profile of the patients were done at recruitment and on the third visit (after six months). There was no significant change in the Lipid profile from baseline (first visit). Only two female patients had a marginally raised low-density lipoprotein (LDL) cholesterol on the third visit. All the patients were on standard doses of statins (Atorvastatin / Rosuvastatin) throughout the study.

	Switched from Dapagliflozin		Intra Group p-value
	First Visit	Third Visit	
Mean HbA1c (%)	**6.65**	**6.67**	0.8620
Mean S.B.P (in mmHg)	**121.53**	**115.84**	0.0396
Mean D.B.P (in mmHg)	**72.30**	**66.61**	0.0136
Mean Body weight (Kg)	**66.15**	**68.38**	0.3314
Mean eGFR(ml/min/1.73m^2)	**75.76**	**74.38**	0.6671
SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure			

Table 1: Mean values of glycemic and extraglycemic parameters of patients switched from Dapagliflozin.

	Switched from Empagliflozin		Intra Group p-value
	First Visit	Third Visit	
Mean HbA1c (%)	**6.70**	**6.93**	0.0047
Mean S.B.P (in mmHg)	**122.21**	**110.10**	<0.0001
Mean D.B.P (in mmHg)	**71.26**	**64.47**	0.0003
Mean Body weight (Kg)	**70.63**	**66.52**	0.0077
Mean eGFR(ml/min/1.73m^2)	**79.89**	**78.89**	0.7150
SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure			

Table 2: Mean values of glycemic and extraglycemic parameters of patients switched from Empagliflozin.

Discussion

This was a single centre, non-randomized retrospective real-world study done to evaluate the efficacy of Remogliflozin etabonate, a cheaper SGLT2 inhibitor available in India, compared with costlier SGLT2 inhibitors, Dapagliflozin and Empagliflozin. Overall, there were no clinically relevant or significant changes in therapeutic extraglycemic parameters on initiation of Remogliflozin etabonate, replacing the other SGLT2 inhibitors. SGLT-2 inhibitors are exceptionally versatile to have glycemic and extraglycemic benefits in terms of reducing blood glucose, improving renal function and preventing adverse cardiovascular outcomes [12]. Remogliflozin etabonate is a potent and selective O-glycoside inhibitor of SGLT-2 with a shorter half-life of 1.39 h [13]. Pattanaik SR(2020) found Remogliflozin (100 mg BD) to be significantly efficacious as an add on to T2DM patients with inadequate control with Metformin and Glimeperide [14]. Various clinical trials also provide insight into the efficacy and safety of Remogliflozin etabonate.

Mahapatra H, et al. (2022) illustrated the experience of Remogliflozin administered concomitantly with other antidiabetic drugs which was found to be effective and was well tolerated in Indian patients with T2DM [15]. Dharmalingam M, et al. (2020) demonstrated the efficacy, tolerability and noninferiority of Remogliflozin etabonate 100 mg and 250 mg in comparison with Dapagliflozin for glycemic control in T2DM [16]. There were no significant changes in HbA1c found in our study when patients were switched to Remogliflozin etabonate. Bhattacharyya S, et al. (2022) reported statistically significant reduction from baseline, observed in HbA1c (-1.9%, $p<0.0001$) after initiation of the treatment with Remogliflozin etabonate [17]. However, Agrawal P, et al. (2022) found that HbA1c levels increased marginally but significantly in the patients after switching to Remogliflozin from Empagliflozin, Canagliflozin or Dapagliflozin [18].

SGLT2 inhibitors have a favourable impact on weight, blood pressure, dyslipidemia, uric acid concentrations, oxidative stress and inflammation. These drugs cause increased glucose excretion, leading to caloric loss and diuresis with a reduction of body weight and BP [19,20]. They improve endothelial dysfunction and

reduce oxidative stress and inflammation mediated by multiple mechanisms, largely related to their ability to reduce high glucose-induced oxidative stress [21]. SGLT2 inhibitors affect lipid metabolism at different cellular levels resulting in the net increase in LDL level [22]. Bhosle D, et al. (2022) indicated that different SGLT2 inhibitors (Canagliflozin, Empagliflozin , Dapagliflozin, or Remogliflozin) are effective in reducing HbA1c, Fasting Blood Sugar (FBS), Post Prandial Blood Sugar (PPBS), body weight, Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) in Indian patients with T2DM [23]. Nakano S, et al. (2015) determined the oxygen radical absorbance capacity (ORAC) in three different SGLT2 inhibitors (Remogliflozin, Canagliflozin and Dapagliflozin) in a diet-induced obese mouse model of non-alcoholic fatty liver disease and found that only Remogliflozin had significant ORAC activity [24]. Pattanaik SR, et al. (2022) determined that Remogliflozin has a statistically significant effect on reduction of weight, BMI, and diastolic blood pressure [25]. In this study also, there were no significant changes in HbA1c, eGFR values and lipid profile from baseline on initiation of remogliflozin replacing other SGLT2 inhibitors. However, the reduction in blood pressure and body weight was statistically significant for patients switched from Empagliflozin ($p<0.01$).

Conclusion

Remogliflozin etabonate given as 100 mg twice daily is non-inferior to Empagliflozin 10 mg / Dapagliflozin 10 mg given as once daily to patients of T2DM as far as their glycemic goals are concerned. The extra glycemic effects are favorable with a slight advantage of better blood pressure reduction in comparison to Empagliflozin and Dapagliflozin with a cost burden reduction of more than 50%.

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