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Original Research Article

A real-world clinical experience on the effectiveness of remogliflozin etabonate in management of Indian patients with type II diabetes mellitus

Soumya Sengupta[1]*, Sunita Sengupta[2], Sagar Katare[3]

[1]Diabetic Clinic, Chaibasa, Jharkhand, India
[2]Sambhu Nath Pandit Hospital, Kolkata, West Bengal, India
[3]Glenmark Pharmaceuticals Ltd, Mumbai, Maharashtra, India

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***Correspondence:**
Dr. Soumya Sengupta,
E-mail: saumyasengupta@yahoo.co.in

ABSTRACT

Background: The aim of the study was to evaluate effectiveness and safety of remogliflozin etabonate in a real-world outpatient setting in type 2 diabetes mellitus (T2DM) patients in India.
Methods: A retrospective, observational, single-center study wherein medical records of adult patients (≥18 years old) with T2DM managed with remogliflozin 100 mg for at least three months at the diabetes care center in Jharkhand were retrieved. The effectiveness was assessed in terms of change from baseline in glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), postprandial plasma glucose (PPG), total body weight, blood pressure (BP, systolic and diastolic), kidney function tests, and lipid parameters after three months of treatment. Safety was assessed by adverse events (AEs) and serious AEs.
Results: Half of the patients received ≥3 concomitant antidiabetic drugs, common being sulphonylureas (92%), and metformin (91%). Remogliflozin treatment resulted in a significant mean reduction from baseline in HbA1c [-1.99 (0.12%); p<0.001], FPG [-52.3 (4.31) mg/dl; p<0.001] and PPG [-103.6 (7.10) mg/dl; p<0.001). Bodyweight reduction was not statistically significant [-0.1 (10.12) kg]. A significant reduction was observed in the systolic BP [-15.9 (2.21) mmHg; p<0.001] and diastolic BP [-3.3 (0.95) mmHg; p=0.001]. Commonly reported AE was heartburn (51.4%) and urinary tract infections (34.2%). No serious AEs were reported. The mean estimated glomerular filtration rate showed a statistically significant reduction of -1.55 (0.61) ml/min. The lipid parameter findings were non-significant.
Conclusions: The real-world experience of remogliflozin administered concomitantly with other antidiabetic drugs was effective and well-tolerated in Indian patients with T2DM.

Keywords: Glycated hemoglobin, Real-world, Remogliflozin etabonate, Sodium-glucose cotransporter-2 inhibitor, Type 2 diabetes mellitus

INTRODUCTION

Worldwide, half a billion people are living with diabetes, and the prevalence is projected to increase by 51% in 2045.[1] According to the International Diabetes Federation Atlas 2019, among adults aged 20-79 years in India, 77 million (8.9% of the total population) have diabetes, and 43.9 million have undiagnosed diabetes.[2] Thus, there is a need for novel treatment options to manage patients with diabetes effectively. A variety of antidiabetic treatment options are available, however, undesirable side effects such as hypoglycemia, weight gain due to hyperinsulinemia, gastrointestinal symptoms, and hepato-renal toxicity are commonly observed.[3,4] Metformin,

considered as the first line treatment option for T2DM patients, may not be highly effective for glycemic control as a monotherapy; hence, a combination with other glucose-lowering drugs may be required.[2,5-9]

The sodium-glucose cotransporter-2 inhibitors (SGLT2i or gliflozins) are a new class of anti-diabetes drugs for patients with T2DM with unique insulin-independent renal action that assist in decreasing body weight by increasing glucose excretion, increasing insulin sensitivity, reduction in blood pressure (BP) and arterial stiffness, amongst others.[10] Thus, SGLT2i can act as an adjuvant to other antidiabetic drugs.[11-13] SGLT2i has been known to reduce HbA1c by 0.5-1.0% (5.5-11 mmol/mol) versus placebo.[14,15] Their mode of action is independent of insulin and, thus, can be used at any stage of T2DM.[16] The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend SGLT2i for patients with diabetes having cardiovascular and chronic renal comorbidities.[2] In a recent evidence-based consensus report on the positioning of SGLT2i amongst T2DM patients in India, its use is recommended due to multiple clinical benefits.[17]

Remogliflozin etabonate is a potent and selective SGLT2i recently approved in India for the treatment of patients with T2DM.[18,19] It has a short elimination half-life and is dosed twice-daily (BID) to obtain 24-hour glucose-lowering effects compared with other approved SGLT2i.[20-24] A recent 24-weeks, randomized, double-blind, pivotal study by Dharmalingam et al described the efficacy and safety of different doses of remogliflozin and demonstrated non-inferiority versus other SGLT2i thereby establishing remogliflozin as an efficacious and well-tolerated treatment option for glycemic control in Indian T2DM patients.[18] As remogliflozin has been introduced recently for clinical use in India, the evidence for real-world clinical effectiveness of remogliflozin in T2DM patients remains limited. Real-world evidence plays an important role in understanding the usefulness of medical treatments in a broader patient population compared to a clinical trial setting. Such real-world evidences provide essential details on the long-term safety and effectiveness of a therapy and provide key insights into treatment effects in a more naturalistic setting. The aim of the study therefore was one among the first real-world evidence with remogliflozin in Indian patients with T2DM, which evaluated the effectiveness and safety of the drug as an add on therapy to the existing antidiabetic drugs.

METHODS

Study design

With the objective to assess the effectiveness and safety profile, this study was planned as a retrospective, observational, single-center, real-world study at Dr. Soumya Sengupta's Diabetic Clinic, Jharkhand. The analysis included clinical data from medical records of Indian T2DM patients managed at the diabetes care center in Jharkhand state that was retrieved between January to March 2020. The study was conducted as per Indian Council of Medical Research National Ethical Guidelines for Biomedical and Health Research involving human participant, 2017.

Patient cohort

From the medical records of patients treated at the centre, the medical records of patients with T2DM were screened who had uncontrolled levels of HbA1c (>7.0%), treated with remogliflozin based regimen and had completed follow-up visit after 3 months from initiation of remogliflozin based therapy. The records of patients with evidence of active urinary tract infection (UTI) or recorded estimated glomerular filtration rate (eGFR) <45 ml/min on the day of initiation of remogliflozin etabonate were excluded. The first 100 eligible patients records having all parameters of the endpoints discussed later were considered for further study analysis.

Study treatment

Patients who received remogliflozin etabonate for their routine management as per clinical requirements were selected. All T2DM patients received 100 mg of remogliflozin etabonate BID over the 3-months observation period. Besides, any concomitant antidiabetic drugs administered, such as oral hypoglycemic agents and insulin, were recorded. Patients received remogliflozin etabonate as per the clinical needs based on the physician's discretion.

Data collection

The day of initiation of remogliflozin etabonate was considered as index date (day 0/baseline) for each patient. The clinical data from medical records of eligible patients was captured in data record sheet for baseline and follow-up data 3 months from the index date. The data was captured in de-identified fashion to ensure patient confidentiality by a site personnel and verified by independent reviewer for accuracy. The data captured included demographics viz. patient's age, gender, family history of T2DM, duration of T2DM, comorbid conditions at baseline, and concomitant medications for T2DM along with modifications made during the observation period of 3 months. The clinical parameters captured at both baseline and follow-up included measurement of body weight, systolic and diastolic blood pressure (SBP and DBP), laboratory assessment of HbA1c, fasting plasma glucose (FPG), postprandial plasma glucose (PPG), hemoglobin (Hb), hematocrit test (HCT), lipid parameters [total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG)], HDL-C/LDL-C ratio, and kidney function tests [eGFR, serum creatinine, urine albumin-to-creatinine ratio (UACR), and serum uric acid]. The

adverse events (AEs) in terms of symptoms, signs or abnormal laboratory parameters as recorded in patient medical records were captured for safety assessment.

Outcomes

The study intended to assess the effectiveness as well as the safety of remogliflozin in a real-world setting. The endpoints to assess clinical effectiveness of glycaemic control included mean change from baseline in HbA1c FPG, PPG at the end of 3 months and the proportion of patients achieving target HbA1c (<7%). The endpoints assessment of clinical effectiveness in non-glycemic effects included mean change at 3 months from baseline in total body weight, SBP, and DBP. The other exploratory endpoints considered were mean change from baseline in hemoglobin and hematocrit levels, UACR and serum uric acid levels. The safety endpoints included incidences of AEs concerning abnormal symptoms, vital signs, or abnormal laboratory tests as recorded in medical records. The safety was also assessed using the mean change from baseline observed in eGFR, serum creatinine levels and fasting lipids *viz.* TG, TC, LDL-C, HDL-C and lipid ratio of HDL-C/LDL-C.

Statistical analysis

Summary statistics for quantitative variables included the number of observations (n), mean, and standard deviation (SD). Continuous variables were presented as means (SD) and categorical variables as frequencies and percentages. Data are presented as mean (SD) unless otherwise specified. Primary and secondary quantitative variables for changes from baseline to month 3 were analyzed using a paired t-test at 5% level of significance with two-sided 95% confidence intervals (CI); $p<0.05$ was considered statistically significant. Effectiveness analysis set included all patients whose baseline and follow-up assessment data were available. Safety analysis set included all patients in whom at least one dose of medication was administered.

The safety data were summarized descriptively. Laboratory evaluations were summarized with descriptive statistics, and change from baseline was summarized for each post-baseline visit. Descriptive statistics were used for vital sign findings. Statistical analyses were performed using MS excel for descriptive statistics, and a paired t-test was analyzed using GraphPad Prism Version 8.0.

RESULTS

The first 100 eligible medical records were considered for study analysis.

Demographics and patient characteristics

The mean (SD) age and duration of T2DM patients was 53.6 (10.65) years and 6.5 (5.01) years, respectively with male preponderance observed (62%). Approximately one-third (34%) patients had positive family history of T2DM. Of the total patients, 43% had comorbid conditions, the most common being hypertension (39%) followed by neuropathy (17%).

Almost half (49%) of the patients were receiving three concomitant anti-diabetic drugs and additional 37% of patients were on ≥4 concomitant medication along with remogliflozin. The most common concomitant medications were sulphonylureas (92%) and metformin (91%) while 16% of patients received insulin therapy. The mean (SD) baseline characteristics concerning HbA1c, FBG, PPG, body weight, SBP and DBP, and eGFR were 9.8 (1.63%), 155.9 (49.61) mg/dl, 289.3 (80.62) mg/dl, 66.9 (11.04) kg, 145 (25.18) mmHg, 82.1 (11.25) mmHg, and 76.6 (10.1) ml/min, respectively.

The details of baseline demographics and characteristics are shown in Table 1.

Table 1: Demographics and patient baseline characteristics (Safety set).

Parameters	Remogliflozin etabonate (N=100)
Age (years) mean (SD)	53.61 (10.65)
Men, n (%)	62 (62)
Women, n (%)	38 (38)
Body weight (kg) mean (SD)	66.89 (11.04)
HbA1c (%), mean (SD)	9.81 (1.63)
Duration of diabetes (years)	6.52 (5.01)
Family history, n (%)	34 (34)
Comorbid conditions, n (%)	43 (43)
Hypertension	39 (39)
Peripheral artery disease	11 (11)
Neuropathy	17 (17)
Chronic kidney disease	2 (2)
Dyslipidemia	2 (2)
Foot ulcer	2 (2)
Oral antidiabetics	1 (1)
Concomitant medications, n (%)	
1 conmed	7 (7)
2 conmeds	7 (7)
3 conmeds	49 (49)
>3 conmeds	37 (37)
Antidiabetic drug class	
Sulphonylureas	92 (92)
Biguanides (metformin)	91 (91)
Gliptins	56 (56)
Thiazolidinediones	49 (49)
Alpha-glucosidase inhibitor	15 (15)
Insulin	16 (16)

Safety set included all patients in whom at least one dose of medication was administered. BD- twice a day; OD- once a day; SD- standard deviation.

Effectiveness outcomes

At 3 months after initiation of remogliflozin, a clinically significant reduction in mean (SD) HbA1c from 9.8% (1.63)% at baseline to 7.8 (1.19)%, was statistically significant [-1.99% (1.23); p<0.001; Figure 1].

Similarly, statistically significant improvements were observed in mean FPG from 156 (49.61) mg/dl at baseline to 103.7 (12.34) mg/dl [-52.3 (43.13) mg/dl; p<0.001] and PPG from 289.3 (80.62) mg/dl at baseline to 185.7 (28.26) mg/dl [-103.6 (71.04) mg/dl; p<0.001] (Table 2, Figure 2).

The bodyweight reduction of -0.1 (1.18) kg was clinically as well as statistically non-significant (p=0.6309) (Table 2, Figure 3). A total of 24% of T2DM patients achieved the target HbA1c (<7%) in the analysed cohort.

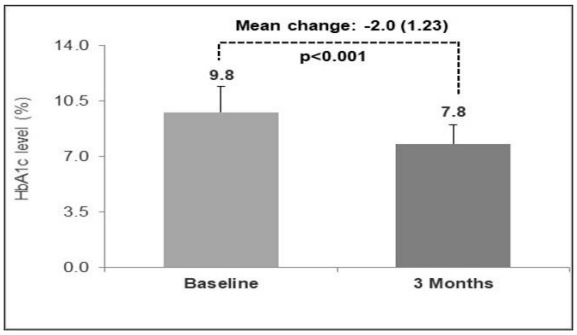

Figure 1: Mean HbA1c levels and change from baseline to month 3 in patients with T2DM (Effectiveness set).

In Figure 1, effectiveness analysis set included all patients whose baseline as well as 3-month follow-up assessment data were available; HbA1c, glycated haemoglobin.

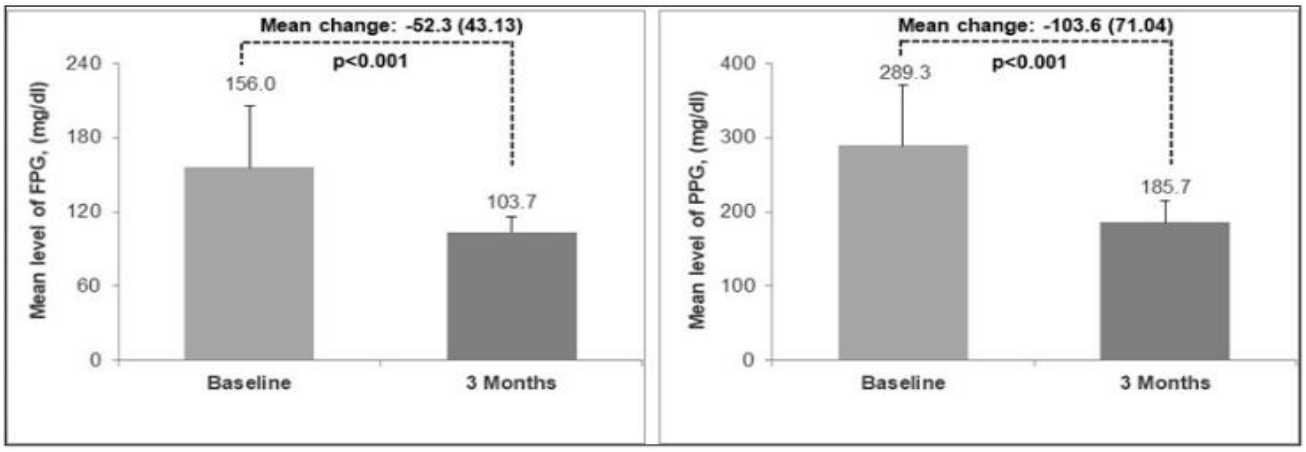

Figure 2: Mean levels of FPG and PPG concentrations and change from baseline to month 3 in patients with T2DM (Effectiveness set).

In Figure 2, effectiveness analysis set included all patients whose baseline as well as 3-month follow-up assessment data were available; FPG, fasting plasma glucose; PPG, postprandial plasma glucose.

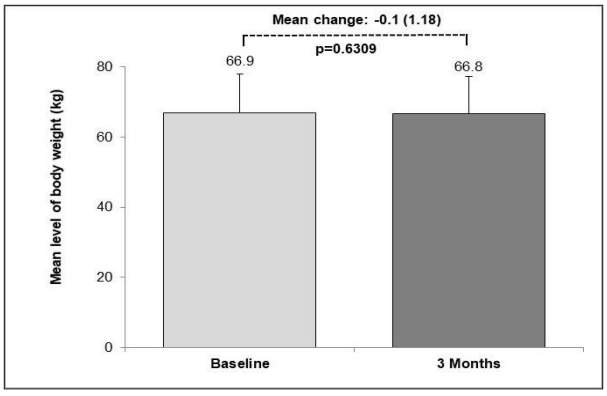

Figure 3: Mean level of body weight and change from baseline to month 3 (Effectiveness set).

In Figure 3, effectiveness analysis set included all patients whose baseline as well as 3-month follow-up assessment data were available.

Likewise, a statistically significant mean (SD) reduction of -15.9 (22.11) and -3.3 (9.53) mmHg (p<0.01 for both) from baseline of 145.01 (25.2) and 82.11 (11.26) mmHg was observed in SBP and DBP respectively, at 3 months.

The Hb and hematocrit levels both showed a mean (SD) increase from baseline of 11.8 (1.18) g% and 45 (2.85)% to 12.6 (4.98) g% and 48.8% (25.42), respectively. The mean (SD) from baseline viz. 0.8 (4.99) g% for Hb and 3.7 (25.72)% for Hct were both found to be statistically insignificant (Table 2).

The serum uric acid and UACR showed inconsequential changes in mean (SD) from baseline of 6.4 (0.83) mg/dl and 32.8 (17.62) to 6.4 (0.77) mg/dl and 33.0 (17.6) respectively (Table 2).

Safety outcomes

A total of 35 AEs was observed in 21 patients over the study, with 11 patients having more than 1 AE reported. The most commonly reported AEs were heartburn (18%), followed by UTI (12%) and headache (5%). All the AEs were either mild (19, 54.3%) or moderate (16, 45.7%) and did not require remogliflozin discontinuation. No incidents of hypoglycemia and serious adverse events were reported. The mean eGFR showed a reduction from baseline 76.58 (10.09) ml/min to month 3 [75.03 (8.97) ml/min], a mean change of -1.55 (0.61) ml/min, which was statistically significant (p=0.012). The change in serum creatinine level however was non-significant from baseline 0.922 (0.232) mg/dl to month 3 [0.957 (0.184) mg/dl].

The lipid levels of TC, TG, LDL-C, HDL-C showed non-significant mean changes from the baseline at month 3 of 0.0 (27.34) mg/dl, -3.2 (25.09) mg/dl, 0.0 (5.40) mg/dl, and 2.0 (9.66) mg/dl, respectively. The lipid ratio of HDL-C/LDL-C showed insignificant change from baseline of 0.36 (0.07) and 0.39 (0.11), respectively (Table 2).

Table 2: Mean change from baseline in glycemic and non-glycemic parameters (Effectiveness set).

Parameters	Remogliflozin etabonate (N=100)		
	Baseline	At 3 month	Mean change from baseline, p value
Glycemic			
HbA1c (%)*	9.8 (1.63)	7.8 (1.20)	-2.0 (1.23), p<0.001
Fasting plasma glucose (mg/dl)	156.0 (49.61)	103.7 (12.34)	-52.3 (43.13), p<0.001
Postprandial blood glucose (mg/dl)	289.3 (80.62)	185.7 (28.26)	-103.6 (71.04), p<0.001
Others			
Total body weight (kg)	66.9 (11.04)	66.80 (10.60)	-0.1 (1.18), p=0.6309
Systolic BP (mmHg)	145.0 (25.18)	129.1 (9.74)	-15.9 (22.11), p<0.001
Diastolic BP (mmHg)	82.1 (11.26)	78.9 (5.07)	-3.3 (9.53), p=0.001
Hemoglobin (g%)	11.8 (1.18)	12.6 (4.98)	0.8 (4.99), p=0.1003
Hematocrit (%)	45.0 (2.85)	48.8 (25.42)	3.7 (25.72), p=0.1514
Serum uric acid (mg/dl)	6.4 (0.83)	6.4 (0.77)	0.0 (0.64), p=0.709
UACR	32.8 (17.6)	33.0 (17.6)	0.2 (1.92), p=0.930
eGFR (ml/min)	76.6 (10.09)	75.0 (8.97)	-1.55 (6.09), p=0.0123
Serum creatinine (mg/dl)	0.92 (0.23)	0.96 (0.18)	0.04 (0.14), p=0.242
Lipid			
Total cholesterol (mg/dl)	208.5 (38.42)	208.0 (33.84)	0.0 (27.34), p=0.998
Triglycerides (mg/dl)	199.7 (37.77)	196.5 (39.88)	-3.2 (25.09), p=565
HDL-C (mg/dl)	37.6 (4.07)	39.6 (10.12)	2 (9.66), p=0.075
LDL-C (mg/dl)	102.5 (9.89)	102.5 (10.25)	0.0 (5.40), p=0.998
HDL-C/LDL-C ratio	0.36 (0.07)	0.39 (0.11)	0.03 (0.11), p=0.183

*n=99; Data are presented as mean (standard deviation) unless otherwise specified.
Effectiveness analysis set included all patients whose baseline as well as 3-month follow-up assessment data were available BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

DISCUSSION

Our study is among the first real-world observational findings of remogliflozin in Indian patients with T2DM in an outpatient setting. The findings demonstrate that 3-month treatment with remogliflozin resulted in a significant mean reduction in all glycemic parameters. Though body weight showed no mean reduction; the SBP showed unexpectedly high reduction, with expected significant DBP reduction from baseline. Among exploratory endpoints, though non-significant, positive trend of increase in Hb and HCT values were observed whereas serum uric acid and UACR showed inconsequential changes. No severe or new safety findings were identified. While eGFR was expectedly reduced at Month 3 compared to baseline, the change in serum creatinine was non-significant. No significant impact was observed on lipid profiles after 3 months of treatment.

The population in the study was complex with respect to the management of diabetes considering high glycemic status at baseline wherein 86% of patients were receiving at least 3 concomitant medications during initiation of remogliflozin. This highlights the challenges in managing such interdisciplinary group of patients who are on other antidiabetic drugs and the need for glycemic goals in such patients. The mean HbA1c level achieved after three months of remogliflozin treatment in our study was 7.82% (mean reduction of 1.99%), closer to the target normal levels recommended by the ADA, and that by the Indian Council of Medical Research guidelines for the management of T2DM patients (<7%).[25,26] Our HbA1c findings are consistent with findings in the two trials that

studied the safety and efficacy of remogliflozin [500 mg once daily (QD) or 250 mg BID] and showed significant reductions in HbA1c levels (0.5-1.0%) versus placebo over three months, with improved efficacy when remogliflozin was administered BID.[27,28] The HbA1c reductions in our study were higher than reported recently by Dharmalingam et al.[18] In this study, HbA1c reductions at the end of 3-month was 0.72% in T2DM patients with uncontrolled hyperglycemia on metformin monotherapy who were administered remogliflozin 100 mg BID. In another observational prospective longitudinal study, conducted in an outpatient department of endocrinology and diabetes at a tertiary care center in Indian patients with T2DM, mean reduction in HbA1c at 3-6 months was 1.26%, and 37.4% of patients achieved HbA1c ≤7% at 9-12 months follow-up period.[29] While 24% of T2DM patients achieved the target HbA1c (≤7%) in our study, the same was achieved by 19.6-22.6% of Japanese patients with the use of other SGLT2i at 12 months, and by 26.5% of patients in a retrospective, real-world, observational study in T2DM patients in Thailand over 16 months follow-up.[30,31] Likewise HbA1c, statistically significant improvements were observed with FPG (52.3 mg/dl) and PPG (103.6 mg/dl) in our study. These improvements were much higher than that reported by Dharmalingam et al at week 24 with remogliflozin 100 mg (17.86 mg/dl and 39.2 mg/dl).[18] The significant decrease in glycemic levels in our study could be related to higher baseline HbA1c value (9.82%), a concept that has been discussed previously.[32,33] A positive correlation has been noted between baseline HbA1c and subsequent changes in HbA1c levels.[34] Moreover, ours being a real-world study, the management of T2DM patients was as per clinical needs attributed to the therapeutic interventions administered based on investigator's clinical judgement. This also highlights the usefulness of remogliflozin as an add on therapy with other anti-diabetic drugs in real-world clinical practice. Therefore, the glycemic control obtained with remogliflozin in our study was similar or better versus the reduction observed in real-world studies of other SGLT2i making this drug comparable to other SGLT2i for management of T2DM patients in India.

While HbA1c reductions were significant, the mean body weight change from baseline to Month 3 in our study was non-significant (-0.1 kg) i.e. from 66.89 (11.04) kg at baseline to 66.83 (10.59) kg at month 3. Dharmalingam et al reported significant weight reductions with remogliflozin 100 mg and 250 mg (-2.94 and -3.17 kg) at month 3 from baseline.[18] Significant reductions in body weight were observed by Sykes et al. ranging from 1.36-3.51 kg at week 12 in patients receiving remogliflozin compared with placebo.[28] Vishwanathan et al reported the mean change in body weight with other SGLT2i at the same time point to be statistically significant (1.14 kg) i.e. from 78.15 kg (13.48) at baseline to 77.01 kg (13.21) at month 3.[35] The real-world retrospective study in Thailand showed the weight reduction with SGLT2i from 78.2 kg at baseline to 76 kg at month 3.[31] In the observational outpatient study in India, there was significant reduction in weight from baseline (89.32 kg), with mean weight loss of 3.2 kg at 3-6 months.[29] Thus, in comparison to other real-world findings, the lower weight reduction in our setting could be possibly attributed to; firstly, lower weight at baseline and secondly, concomitant sulphonylurea in 92% of patients which is known to cause weight gain.

Significant reductions were observed in SBP (-15.9 mmHg) and DBP (-3.3 mmHg) from baseline to month 3 in our study. The real-world study in Thailand showed the reductions in SBP and DBP from baseline to Month 18 with mean SBP reduction of 8.2 mmHg and DBP reduction of 3.6 mmHg.[31] The reductions in both SBP and DBP reported by Dharmalingam et al with remogliflozin 100 mg and 250 mg, at month 6, were (-2.6 mmHg and -2.0 mmHg) and (-2.6 mmHg and -0.7 mmHg), respectively.[18] Vishwanathan et al showed the mean decrease in SBP and DBP from baseline at month 3 to be 3.24 mmHg and 1.13 mmHg using other SGLT2i.[35] It is important to note that higher reductions in BP in our study can be attributed to the fact that 39% of patients were hypertensive and received anti-hypertensive drugs as per clinical needs. The significant reduction could therefore be attributed to concomitant use of anti-hypertensive drugs. Overall, it can be reasonably acknowledged that real-world findings with remogliflozin in our study showed comparable outcomes in glycemic and non-glycemic parameters compared with SGLT2i.

The safety and tolerability of remogliflozin were in line with the known safety profile of SGLT2i.[13,36] UTI was observed in 12% of patients in our study. Dharmalingam et al reported UTIs in 2.1-6.6% of patients with most patients experiencing only one incidence.[18] Interestingly, Vishwanathan et al reported UTIs in only 0.2% of T2DM patients with other SGLT2i, all AEs being mild in intensity.[35] In the prospective, observational study in India with other SGLT2i, 10.8% females and 4.8% males suffered from UTI.[29] Leiter et al demonstrated only one patient with severe UTI on 100 mg canagliflozin, and mild UTI episodes reported in 10.6%.[37] Recent post-hoc analysis of canagliflozin showed a trend toward higher rate of UTI in hot climate countries when compared with other areas (9.5% vs 4.6% at 26 weeks of placebo-controlled period, 22.3% vs 7.4% at 104 weeks of active controlled period with canagliflozin 100 mg).[38] In another real-world cohort study utilizing patient data obtained from a large health plan database from an outpatient clinic in Mexico with other SGLT2i, a higher frequency of UTI [Odds ratio: 2.3, 95% CI (1.81, 2.78)] was reported.[39] However, possible reason for marginally higher UTI incidence in our study could be high HbA1c levels causing proportional high glucosuria, which can be considered medically plausible though has no evidence yet.

The mean eGFR in our study showed significant reduction of -1.55 (0.61) ml/min at 3 month. The reduction however can be considered clinically insignificant on background of baseline eGFR of 76.6 ml/min and minimal change in serum creatinine. Dharmalingam et al showed no clinically

relevant difference in eGFR and serum creatinine level with the use of remogliflozin 100 mg and 250 mg suggestive of recovery in eGFR by 6 months.[18] The real-world study in Thailand utilizing other SGLT2i showed no change in eGFR rate before and after treatment (83 ml/min/1.73 m^2 vs 82 ml/min/1.73 m^2).[31] Regarding the lipid parameters, the TC, TG, LDL-C, and HDL-C, HDL-C/LDL-C values in our study showed non-significant changes from the baseline to month 3. Contrary to our study findings, Sykes et al reported increased serum LDL-C concentrations from baseline, with an increase in TC and HDL-C concentrations and a decreasing trend in TG concentrations at week 12.[28] Nevertheless, our study findings were aligned with Dharmalingam et al where remogliflozin 100 mg and 250 mg demonstrated comparable effects in reducing TC, LDLC, and TG after 24 weeks.[18] Overall, with no reported incidences of hypoglycemia and serious adverse events during our study, it is reasonable to consider remogliflozin being well-tolerated in Indian patients with T2DM.

The real strength of our study was this being the first real-world experience on the use of remogliflozin in T2DM patients in India.

Limitations

Our study findings should be interpreted by keeping a few limitations in mind, such as a convenient sampling method and being a single-center study; the results cannot be extrapolated to a broader T2DM population. There was no control arm included in the study, which could thus, not be useful in estimating the actual treatment effect. Most importantly, the overall beneficial effects of remogliflozin may not also be pertaining to its usage as a monotherapy and should consider concomitant administration effects of the other antidiabetic drugs. Nevertheless, caution should be exercised while comparing studies with other SGLT2i considering the differences in study design, population, study duration, and related comparators. Just like in any real-world, one also needs to be conscious of the presence of confounders and biases.

CONCLUSION

To conclude, this real-world clinical experience of remogliflozin 100 mg combined with other antidiabetic drugs demonstrated to be an effective, and well-tolerated option in the management of Indian patients with T2DM. The treatment showed significant improvements in glycemic parameters by month 3, making it comparable to other SGLT2i for management of T2DM patients in India. Future long-term real-world clinical studies are needed to validate the findings across a broader patient population.

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REFERENCES

1. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract. 2019;157:107843.
2. International Diabetes Federation. IDF Diabetes Atlas 9th edition; 2019. Available at: https://www.diabetesatlas.org/enresources. Accessed on 10 March 2021.
3. Dey L, Sttele AS, Yuan C. Alternative therapies for type 2 diabetes. Altern Med Rev. 2002;7:45-58.
4. Choi CI. Sodium-Glucose co-transporter 2 (SGLT2) inhibitors from natural products: discovery of next-generation antihyperglycemic agents. Molecules. 2016;21:1136.
5. International Diabetes Federation. Global guideline for type 2 diabetes, 2012. Available at: https://www.iapb.org/wpcontent/uploads/GlobalGuideline-for-Type-2-Diabetes-IDF-2012. Accessed on 10 March 2021.
6. National Institute for Health and Clinical Excellence. Type 2 diabetes: The Management of type 2 diabetes (NICE clinical guideline 87), 2009. Available at: https://www.nice.org.uk/guidance/ta203/documents/nicerecommendsfortype-2diabetesmellitus.Accessed on 10 March 2021.
7. Irons BK, Minze MG. Drug treatment of type 2 diabetes mellitus in patients for whom metformin is contraindicated. Diabetes Metab Syndr Obes. 2014;7:15-24.
8. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2012;35(6):1364-79.
9. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, et al. American Association of Clinical Endocrinologists' comprehensive diabetes management algorithm 2013 consensus statement. Endocr Pract. 2013;19:1-48.
10. Kalra S, Ghosh S, Aamir AH, Ahmed M, Amin MF, Bajaj S, et al. Safe and pragmatic use of sodium–glucose co-transporter 2 inhibitors in type 2 diabetes

mellitus: South Asian Federation of Endocrine Societies consensus statement. Indian J Endocr Metab. 2017;21:210-30.
11. Abdul GMA, Norton L, Fronzo RA. Efficacy and safety of SGLT2 inhibitors in the treatment of type 2 diabetes. Curr Diabetes Rep. 2012;12:230-8.
12. Vallon V. The mechanisms and therapeutic potential of SGLT2 inhibitors in diabetes mellitus. Annu Rev Med. 2015;66:255-70.
13. Hsia DS, Grove O, Cefalu WT. An update on sodium-glucose co-transporter-2 inhibitors for the treatment of diabetes mellitus. Curr Opin Endocrinol Diabetes Obes. 2017;24:73-9.
14. Vasilakou D, Karagiannis T, Athanasiadou E, Mainou M, Liakos A, Bekiari E, et al. Sodium-glucose co-transporter 2 inhibitors for type 2 diabetes: a systematic review and metaanalysis. Ann Intern Med. 2013;159:262-74.
15. Stenlof K, Cefalu WT, Kim KA, Alba M, Usiskin K, Tong C, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetes Obes Metab. 2013;15:372-82.
16. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient Centered Approach. Diabetes Care. 2015;38:140-49.
17. Singh AK, Unnikrishnan AG, Zargar A, Kumar A, Das AK, Saboo B, et al. Evidence-Based Consensus on Positioning of SGLT2i in Type 2 Diabetes Mellitus in Indians. Diabetes Ther. 2019;10:393-428.
18. Dharmalingam M, Aravind SR, Thacker H, Paramesh S, Mohan B, Chawla M, et al. Efficacy and Safety of Remogliflozin Etabonate, a New Sodium Glucose Co-Transporter-2 Inhibitor, in Patients with Type 2 Diabetes Mellitus: A 24-Week, Randomized, Double-Blind, Active-Controlled Trial. Drugs. 2020;80(6):587-600.
19. Mohan V, Mithal A, Joshi SR, Aravind SR, Chowdhury S. Remogliflozin Etabonate in the Treatment of Type 2 Diabetes: Design, Development, and Place in Therapy. Drug Des Devel Ther. 2020;14:2487-501.
20. Heise T, Seewaldt BE, Macha S, Hantel S, Pinnetti S, Seman L, et al. Safety, tolerability, pharmacokinetics and pharmacodynamics following 4 weeks' treatment with empagliflozin once daily in patients with type 2 diabetes. Diabetes Obes Metab. 2013;15:613-21.
21. Heise T, Seman L, Macha S, Jones P, Marquart A, Pinnetti S, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple rising doses of empagliflozin in patients with type 2 diabetes mellitus. Diabetes Ther. 2013;4(2):331-45.
22. Kasichayanula S, Liu X, Lacreta F, Grifen SC, Boulton DW. Clinical pharmacokinetics and pharmacodynamics of dapagliflozin, a selective inhibitor of sodium-glucose co-transporter type 2. Clin Pharmacokinet. 2013;53:17-27.
23. Devineni D, Polidori D, Curtin C, Stieltjes H, Tian H, Wajs E. Single-dose pharmacokinetics and pharmacodynamics of canagliflozin, a selective inhibitor of sodium-glucose co-transporter 2, in healthy Indian participants. Clin Ther. 2016;38:89-98.
24. Kapur A, Connor SR, Hussey EK, Dobbins RL, Tao W, Hompesch M, et al. First dose-escalation study with remogliflozin etabonate, a selective inhibitor of the sodium-glucose transporter 2 (SGLT2), in healthy subjects and in subjects with type 2 diabetes mellitus. BMC Pharmacol Toxicol. 2013;14:26.
25. American Diabetes Association. Glycemic Targets: Standards of Medical Care in Diabetes-2019. Diabetes Care. 2019;42(1):61-70.
26. Indian Council of Medical Research. Guidelines for the management of type 2 diabetes patients, 2018. Available at: https://medibulletin.com/wp-content/uploads/2018/05/ICMR.diabetesGuidelines. 2018. Accessed on 10 August 2020.
27. Sykes AP, Kemp GL, Dobbins R, Connor SR, Almond SR, Wilkison WO, et al. Randomized efficacy and safety trial of once-daily remogliflozin etabonate for the treatment of type 2 diabetes. Diabetes Obes Metab. 2015;98-101.
28. Sykes AP, Connor SR, Dobbins R, Dorey DJ, Lorimer JD, Walker S, et al. Randomized trial showing efficacy and safety of twice-daily remogliflozin etabonate for the treatment of type 2 diabetes. Diabetes Obes Metab. 2015;17:94-7.
29. Gill HK, Kaur P, Mahendru S, Mithal A. Adverse Effect Profile and Effectiveness of Sodium Glucose Co-transporter 2 Inhibitors (SGLT2i) - A Prospective Real-world Setting Study. Indian J Endocrinol Metab. 2019;23:50-5.
30. Ito Y, Schyndle JV, Nishimura T, Sugitani T, Kimura T. Real-World Effectiveness of Sodium Glucose Co-Transporter-2 Inhibitors in Japanese Patients with Diabetes Mellitus. Diabetes Ther. 2019;10:2219-31.
31. Thewjitcharoen Y, Yenseung N, Malidaeng A, Nakasatien S, Chotwanvirat P, Krittiyawong S, et al. Efectiveness of long-term treatment with SGLT2 inhibitors: real-world evidence from a specialized diabetes center. Diabetol Metab Syndr. 2017;9:96.
32. Giugliano D, Maiorino M, Bellastella G, Chiodini P, Esposito K. Relationship of baseline HbA1c, HbA1c change and HbA1c target of <7% with insulin analogues in type 2 diabetes: a metaanalysis of randomised controlled trials. Int J Clin Pract. 2011;65:602-12.
33. Brown RE, Gupta N, Aronson R. Effect of dapagliflozin on glycemic control, weight, and blood pressure in patients with type 2 diabetes attending a specialist endocrinology practice in Canada: a retrospective cohort analysis. Diabetes Technol Ther. 2017;19:685-91.
34. Wilding J, Godec T, Khunti K, Pocock S, Fox R, Smeeth L, et al. Changes in HbA1c and weight, and treatment persistence, over the 18 months following initiation of second-line therapy in patients with type

2 diabetes: results from the United Kingdom Clinical Practice Research Datalink. Bio Med Centr Med. 2018;16:116.
35. Viswanathan V, Singh KP. Use of Dapagliflozin in the Management of Type 2 Diabetes Mellitus: A Real-World Evidence Study in Indian Patients (FOREFRONT). Diabetes Technol Ther. 2019;21(8):415-22.
36. Madaan T, Akhtar M, Najmi AK. Sodium glucose Co Transporter 2 (SGLT2) inhibitors: current status and future perspective. Eur J Pharm Sci. 2016;93:244-52.
37. Leiter LA, Langslet G, Vijapurkar U, Davies MJ, Canovatchel W. Simultaneous reduction in both HbA1c and body weight with canagliflozin versus glimepiride in patients with type 2 diabetes on metformin. Diabetes Ther. 2016;7:269-78.
38. John M, Cerdas S, Violante R, Deerochanawong C, Hassanein M, Slee A, et al. Efficacy and safety of canagliflozin in patients with type 2 diabetes mellitus living in hot climates. Int J Clin Pract. 2016;70:775-85.
39. Tamez PHE, Delgadillo EE, Soni DD, Hernandez CMI, Tamez PAL. SGLT2 inhibitors as add on therapy in type 2 diabetes: a real world study. J Diabetes Metab Disord. 2017;16:27.

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