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AN EVIDENCE-BASED DIABETOLOGICAL RESEARCH STUDY ON THE PHARMACOTHERAPEUTIC PRESCRIPTION PATTERNS AND ADVERSE DRUG REACTIONS MONITORING OF 50 mg OR 75 mg REMOGLIFLOZIN WITH 500 mg METFORMIN COMBINATION TREATMENT, IN GLOBAL TERTIARY CARE HOSPITALS.

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ABSTRACT

Introduction: Remogliflozin, a selective insulin independent sodium glucose co-transporter subtype 2 (SGLT2) inhibitor, inhibits reabsorption of renal glucose, lowers blood sugar, and causes glucosuria, in type II diabetes mellitus patients. Metformin, as a combination anti-diabetic drug, lowers serum glucose levels, by the activation of 5' adenosine monophosphate (AMP) activated protein kinase. **Objectives:** The objective of this evidence-based diabetological research study was the pharmacotherapeutic prescription patterns and adverse drug reactions monitoring of 50 mg or 75 mg remogliflozin with 500 mg metformin combination treatment, in global tertiary care hospitals. **Methods:** 250 new early moderate grade type II diabetes mellitus patients were prescribed oral metformin 500 mg once daily for 30 days. Then, 200 diabetics uncontrolled with metformin monotherapy, were prescribed oral 50 mg remogliflozin with 500 mg metformin once daily, for 15 days; who were subsequently prescribed oral 75 mg remogliflozin with 500 mg metformin once daily for 15 days. The prescription patterns, glycaemic stabilisation rate and the prescription rates of anti-diabetic percentage glycaemic stabilisation of both the anti-diabetic monotherapy and combination therapies provided, were analysed. The percentage of prescriptions of metformin combination therapies, with which glycaemic stabilisation was achieved, as well as the percentage of prescriptions of metformin combination therapies, with which glycaemic stabilisation was not adequately achieved, was calculated. The prescription content analysis, of all the 250 prescriptions, was done. The safety assessment, along with blood sugar and HbA1c levels and urine routine examination, on day 0, day 30, day 46, day 60, and further follow-up, were recorded and statistically analysed. **Results:** Well-controlled glycaemic stabilisation was observed with metformin combination therapies in 198 prescriptions, that is, among 99% patients, whereas glycaemic stabilisation was not adequately controlled with 2 prescriptions, that is, among 1% patients, after 1 month of combination therapies. Prescription content analyses showed 100% completeness, with significant pharmacotherapeutic molecular efficacy. The adverse effects with the combination therapy of 50 mg remogliflozin with metformin and the combination therapy of 75 mg remogliflozin with metformin were statistically non-significant; hence both were safe and tolerable. **Conclusions:** The prescription rates of anti-diabetic percentage glycaemic stabilisation were as follows: prescription percentage of well-controlled glycaemic stabilisation with metformin combination therapies > prescription percentage of inadequate glycaemic stabilisation with metformin combination therapies. The prescription content analyses showed 100% completeness. The combination therapy of 50 mg remogliflozin and metformin as well as the combination therapy of 75 mg remogliflozin and metformin were safe and tolerable.

KEYWORDS: Biguanides, Metformin, Sodium Glucose Co-Transporter Subtype 2 Inhibitors, Remogliflozin, Prescription Patterns, Prescription Content Analysis, Pharmacovigilance, Diabetology.

INTRODUCTION

The American Association of Clinical Endocrinologists (AACE) guidelines for T2DM management, suggest lifestyle therapy, medically assisted weight loss, and individual goals of achieving haemoglobin A1C (HbA1C) level of ≤ 6.5%. The determining factors behind the choice of antidiabetic drugs are the different patient characteristics, like glycaemic index, weight, lifestyle, co-morbidities, and undesirable side effects of pharmaco-therapeutic management.

With remogliflozin, a selective insulin independent sodium glucose co-transporter subtype 2 (SGLT2) inhibitor, the management of type II diabetes mellitus has taken a quantum leap, producing anti-hyperglycaemic activity in both diabetes mellitus type II, and insulin resistant patients, when given in monotherapy or in combination with metformin. Remogliflozin inhibits glucose reabsorption in the kidney, thus lowering blood sugar, and causing glucosuria. Clinical guidelines recommend SGLT2 inhibitors as one of the second-line pharmacological therapeutic approaches, following metformin failure or intolerance. SGLT2 inhibitors cause wider benefits like adequate glycaemic control, significant improvements in haemoglobin A1c, insulin sensitivity and β cell function, weight loss, blood pressure reduction, cardiovascular and renal protection by significantly increasing HDL cholesterol, decreasing LDL cholesterol, reducing albuminuria and delaying the progression of nephropathy. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) suggest the therapeutic use of SGLT2 inhibitors for patients with diabetic co-morbidities like cardiovascular disease (including heart failure, and atherosclerotic cardiovascular disease) and chronic kidney disease.[1, 2]

Metformin, has considerable improved outcomes, as a combination anti-diabetic drug, with pleotropic effects on glucose metabolism. Metformin inhibits hepatic gluconeogenesis in a substrate selective manner, through the transcription, allosteric, substrate availability or redox mechanisms; and by metformin inhibition of complex I leading to reductions in hepatocellular energy charge and other downstream events (eg, adenosine monophosphate–activated protein kinase (AMPK) activation, fructose 1,6-bisphosphatase inhibition, inhibition of glucagon signaling). It overcomes insulin resistance, and lowers serum glucose levels, by the activation of 5' adenosine monophosphate (AMP) activated protein kinase. Metformin alters the cellular redox balance, and the increased cytosolic redox state, due to the inhibition of glycerol-3-phosphate dehydrogenase by metformin. This is observed at clinically relevant concentrations, and is the only proposed mechanism of action that predicts substrate selective (glycerol and lactate) inhibition of hepatic gluconeogenesis. Metformin is both effective and inexpensive, and may reduce the risk of cardiovascular events and death. It has beneficial effects on $HbA1_C$ and weight; and a well-established safety profile.[1,3,4]

The commonly associated side effects with oral anti-diabetic agents are hypoglycaemia, weight gain due to hyperinsulinemia, gastrointestinal symptoms, and hepato-renal toxicity. The critical effects under consideration for the clinical rationale of the anti-diabetic drugs are their potential for hypoglycaemia, weight gain, and long term side effects. This augmentation of adverse effects demands a safer antidiabetic agent. Therefore, this study was conducted as an endocrinological pharmacovigilance study to evaluate the safety involving the clinical therapeutic prescription of anti-diabetic combination therapies, with the escalating doses of remogliflozin: 50 mg remogliflozin and 500 mg metformin, which was subsequently followed by 75 mg remogliflozin and 500 mg metformin, once daily. The successful synergistic effects of these combination therapies and the better drug dose combination regimens, intend to decrease the occurrence of adverse effects, with increased safety and tolerability, thus benefiting the treatment of diabetes mellitus type II. A patient-centered approach was used to guide the choice of pharmacologic agents. The effects of the cardiovascular and renal comorbidities, efficacy, hypoglycaemia risk, impact on weight, cost, risk for side effects, and patient preferences, were also taken into consideration.[1,2,3,4]

OBJECTIVES

The objective of this evidence-based diabetological research study was the pharmacotherapeutic prescription patterns and adverse drug reactions monitoring of 50 mg or 75 mg remogliflozin with 500 mg metformin combination treatment, in global tertiary care hospitals.

METHODS

Ethical Approval

At first, the Institutional Ethics Committee clearance and approval was taken. The study was conducted in accordance with the ethical principles of Declaration of Helsinki and Good Clinical Practices contained within the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH-E6 and ICH-E17), and in compliance with the regulatory requirements. An informed consent was obtained from each patient.

Inclusion Criteria

The inclusion criteria were as follows : (i) patients of any gender, (ii) patients within 35 and 60 years, (iii) patients of around 60 kg average body weight, (iv) patients presenting with new type II diabetes mellitus, of early moderate grade, (v) type II diabetes mellitus American Diabetes Association diagnosis criteria, (vi) co-operative and conscious patients, (vii) patients willing to undergo all pre and post- treatment investigations and willing to complete the entire course of treatment, (viii) patients who have given consent and are willing to go for a follow-up, (ix) patients not taking any previous anti-

diabetic drug, (x) patients not taking any concomitant medication.

Exclusion Criteria
The exclusion criteria were as follows : (i) uncooperative or unconscious patients, (ii) patients below 35 and above 60 years, (iii) patients presenting with any grade other than early moderate grade of diabetes, (iv) patients with a history of hypersensitivity to any of the study drugs, (v) patients with high risk diseases or co-morbidities, (vi) cardiac, renal or any other associated complications or co-morbidities, (vii) any chronic disease intervening with the study data, (x) pregnant or lactating women, (xi) paediatric or geriatric patients, (xii) other associated medical illness or disorders, like uro-genital tract infections, having impact on study results, (xiii) female patients using hormonal contraceptives.

Study Design
A global, multi-centre, prospective, randomized, open-labelled study.

Study Population
The study population was 250 new type II diabetes mellitus patients, of early moderate grade.

Place of Study
The place of research study were the Departments of Pharmacology, Clinical Pharmacology, Molecular Pharmacology, Endocrinology, Diabetology and Metabolic Medicine, Pharmacovigilance, Rational Pharmacotherapeutics, Evidence Based Medicine, Clinical Medicine, Clinical Pathology and Pathology, in Hazra Polyclinic And Diagnostic Centre, Hazra Nursing Home, and Dr. Moumita Hazra's Polyclinic And Diagnostic Centre, and the compilation of the study literature was done in the Departments of Pharmacology, Clinical Pharmacology, and Molecular Pharmacology, in Rama Medical College Hospital and Research Centre, Rama University, GIOSTAR Institute of Regenerative Medicine Institutes, Hospitals and Laboratories, Mamata Medical College, and Mamata Hospitals.

Study Period
The study period was 12 months, from May, 2021 to May, 2022.

Study Procedure
250 new type II diabetes mellitus patients, of early moderate grade, were prescribed oral metformin 500 mg (8.40 mg/kg), once daily, for 30 days. After 1 month, from these 250 patients, 50 diabetic patients : (i) who had achieved adequate glycaemic control with metformin monotherapy, or (ii) who were lost to follow-up, or (iii) who had dropped out due to adverse effects, or (iv) who had withdrawn voluntarily, were excluded from the study. The remaining 200 patients, whose glycaemic index was uncontrolled with metformin monotherapy, were prescribed oral 50 mg (0.84 mg/kg) remogliflozin once daily with 500 mg metformin once daily for 15 days; and were subsequently prescribed oral 75 mg (1.25 mg/kg) remogliflozin once daily with 500 mg metformin once daily for 15 days.

The patient response based on their endocrinological pharmacotherapeutic compliance was thoroughly analysed, by deriving the statistical percentages of the total patients who participated in the study, total patients who completed the study, total patients who were lost to follow-up, total patients who had dropped out due to adverse effects, and total patients who had withdrawn voluntarily, to determine the patient compliance to antidiabetic treatment.

The patients' characteristics, diabetic symptoms assessment, patients' disease and disease-related history were recorded with a proforma. Then, thorough general physical examination and systemic examination were performed on the patients under study. The relevant blood, urine and other investigations were done to confirm the progressing health status of the patients being treated.

The prescription patterns, glycaemic stabilisation rate and the prescription rates of anti-diabetic percentage glycaemic stabilisation of both the anti-diabetic monotherapy and combination therapies provided, were analysed. The number of prescriptions of 250 patients treated with metformin monotherapy as well as remogliflozin and metformin combination therapies were recorded; and the percentage of prescriptions of metformin combination therapies, with which glycaemic stabilisation was achieved, as well as the percentage of prescriptions of metformin combination therapies, with which glycaemic stabilisation was not adequately achieved, was calculated. The prescription content analysis, of all the 250 prescriptions, was done. The different aspects of the prescription contents, like the completeness of the prescription contents, the dose of drug, the duration of treatment, the instructions of medication, the frequency of drug intake, the name of the drug and the dosage form of the drug were thoroughly analysed and recorded, and the various derived observations were statistically analysed as the prescription content analysis percentages.

The efficacy assessment was done, by recording the fasting and the post-prandial blood sugar level, HbA1c level and urine routine examination findings including sugar and albumin levels and microscopy, (a) at baseline level on day 0; (b) after administering metformin monotherapy at day 30; (c) after administering the combination therapy at day 46; (d) after administering the combination therapy at day 60; and (d) further follow-up.

The adverse drug reaction monitoring was done with an Adverse Event Case Report Form, by monitoring the different adverse drug reactions, like hypoglycaemia,

weakness, gastrointestinal disturbances, abdominal pain, and upper respiratory tract infections, after metformin monotherapy, from day 0 to day 30. Then, the adverse drug reaction monitoring was done by monitoring the different adverse drug reactions, like genital mycotic infections, urinary tract infections, pyrexia, headache, dizziness, nausea, gastrointestinal disturbances, hypoglycaemia, weakness or abdominal pain, after the combination therapy of 50 mg remogliflozin once daily with 500 mg metformin once daily, from (i) day 30 to day 46; after the combination therapy of 75 mg remogliflozin once daily with 500 mg metformin once daily; from (i) day 46 to day 60; and (ii) further follow-up.

Statistical Analysis

At the study completion point, the observations recorded in this study, were statistically analysed by the Test of significance with p values, as well as with percentages, with subsequent tabular and graphical representations.

RESULTS

The demographic characteristics of the patients were comparable. 250 new type II diabetes mellitus patients, of early moderate grade, receiving metformin monotherapy, or combination therapy, for 2 months, had completed the study thoroughly, with no adverse effects related drop-out patients, lost to follow-up patients or voluntarily withdrawn patients. As depicted in figure 1, among the 200 patients, whose glycaemic index was uncontrolled with metformin monotherapy, prescribed with oral 50 mg (0.84 mg/kg) remogliflozin once daily with 500 mg metformin once daily for 15 days; and were subsequently prescribed oral 75 mg (1.25 mg/kg) remogliflozin once daily with 500 mg metformin once daily for 15 days, the well-controlled glycaemic stabilisation was observed with the above-mentioned metformin combination therapies in 198 prescriptions, that is, among 99% patients, whereas glycaemic stabilisation was not adequately controlled with 2 prescriptions, that is, among 1% patients, after 1 month of the above-mentioned combination therapies, and they were subsequently transferred to the anti-diabetic combination therapy of 750 mg metformin with 75 mg remogliflozin once daily for the next 15 days.

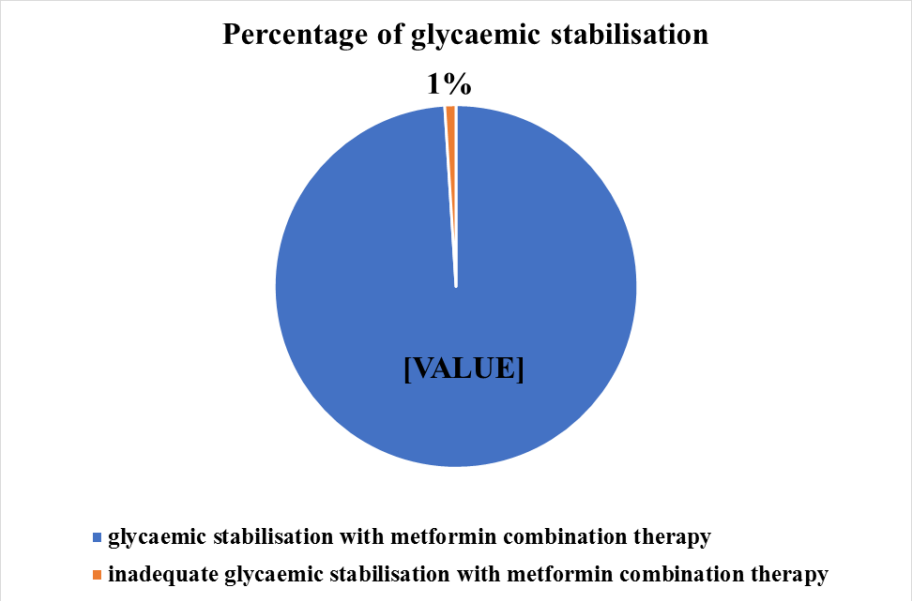

Figure 1: The prescription rates of anti-diabetic percentage glycaemic stabilisation.

Therefore, the prescription rates of anti-diabetic percentage glycaemic stabilisation were as follows: prescription percentage of well-controlled glycaemic stabilisation with metformin combination therapies > prescription percentage of inadequate glycaemic stabilisation with metformin combination therapies.

The completeness of the prescription contents, the dose of drug, the duration of treatment, the instructions of medication, the frequency of drug intake, the name of the drug and the dosage form of the drug were found in 100% of prescriptions, as depicted in table 1.

Table 1: Prescription Content Analysis For Anti-Diabetic Combination Therapies.

Prescription contents	Numbers of Completed Prescriptions	Percentage of Completed Prescriptions
Completeness of prescription Contents	200	100%
Dose of drug	200	100%
Duration of treatment	200	100%
Instruction of medication	200	100%

Frequency of drug intake	200	100%
Name of drug	200	100%
Dosage form of the drug	200	100%

Among 250 new type II diabetes mellitus patients, of early moderate grade, receiving metformin monotherapy for 1 month, 50 diabetic patients : (i) who had achieved adequate glycaemic control with metformin monotherapy, or (ii) who were lost to follow-up, or (iii) who had dropped out due to adverse effects, or (iv) who had withdrawn voluntarily, were excluded from this study. The remaining 200 patients, whose glycaemic index was uncontrolled with metformin monotherapy, received 50 mg remogliflozin with metformin combination therapy, for 15 days, which was subsequently followed by the combination therapy of 75 mg remogliflozin with metformin, for 15 days. These patients had completed the study thoroughly, with no adverse effects related drop-out patients, lost to follow-up patients or voluntarily withdrawn patients.

The combination therapies of 50 mg or 75 mg of remogliflozin and metformin were observed to be safe, which had controlled type II diabetes mellitus among new patients, with significant decrease in the blood sugar levels and the HbA1c levels, within 2 months.

Table 2a: The Occurrence Of Adverse Effects With 50 Mg Remogliflozin And 500 Mg Metformin Combination Therapy.

Adverse effects	Number of patient occurrence	p value
Genital mycotic infections	0	non-significant
Urinary tract infections	0	non-significant
Pyrexia	0	non-significant
Headache	0	non-significant
Dizziness	0	non-significant
Nausea	0	non-significant
Gastrointestinal disturbances	0	non-significant
Hypoglycemia	0	non-significant
Weakness	0	non-significant
Abdominal pain	0	non-significant

Table 2b: The occurrence of adverse effects with 75 mg remogliflozin and 500 mg metformin combination therapy.

Adverse effects	Number of patient occurrence	p value
Genital mycotic infections	0	non-significant
Urinary tract infections	0	non-significant
Pyrexia	0	non-significant
Headache	0	non-significant
Dizziness	0	non-significant
Nausea	0	non-significant
Gastrointestinal disturbances	0	non-significant
Hypoglycemia	0	non-significant
Weakness	0	non-significant
Abdominal pain	0	non-significant

Table 2a depicts the occurrence of adverse effects with 50 mg remogliflozin and 500 mg metformin combination therapy. Table 2b depicts the occurrence of adverse effects with 75 mg remogliflozin and 500 mg metformin combination therapy.

There were no adverse effects observed with the combination therapy of 50 mg remogliflozin with metformin as well as the combination therapy of 75 mg remogliflozin with metformin, which were statistically non-significant. The combination therapy of 50 mg remogliflozin with metformin and the combination therapy of 75 mg remogliflozin with metformin were observed to be safe and tolerable.

DISCUSSION

In this study, the demographic characteristics of the patients were comparable. 250 new type II diabetes mellitus patients, of early moderate grade, receiving metformin monotherapy, or combination therapy, for 2 months, had completed the study thoroughly, with no adverse effects related drop-out patients, lost to follow-up patients or voluntarily withdrawn patients. As depicted in figure 1, among the 200 patients, whose glycaemic index was uncontrolled with metformin monotherapy, prescribed with oral 50 mg (0.84 mg/kg) remogliflozin once daily with 500 mg metformin once daily for 15 days; and were subsequently prescribed oral 75 mg (1.25 mg/kg) remogliflozin once daily with 500 mg metformin once daily for 15 days, the well-controlled

glycaemic stabilisation was observed with the above-mentioned metformin combination therapies in 198 prescriptions, that is, among 99% patients, whereas glycaemic stabilisation was not adequately controlled with 2 prescriptions, that is, among 1% patients, after 1 month of the above-mentioned combination therapies, and they were subsequently transferred to the anti-diabetic combination therapy of 750 mg metformin with 75 mg remogliflozin once daily for the next 15 days. Therefore, the prescription rates of anti-diabetic percentage glycaemic stabilisation were as follows: prescription percentage of well-controlled glycaemic stabilisation with metformin combination therapies > prescription percentage of inadequate glycaemic stabilisation with metformin combination therapies. The completeness of the prescription contents, the dose of drug, the duration of treatment, the instructions of medication, the frequency of drug intake, the name of the drug and the dosage form of the drug were found in 100% of prescriptions. Among 250 new type II diabetes mellitus patients, of early moderate grade, receiving metformin monotherapy for 1 month, the 200 patients, whose glycaemic index was uncontrolled with metformin monotherapy, and thus receiving 50 mg remogliflozin with metformin combination therapy, for 15 days, and subsequently followed by the combination therapy of 75 mg remogliflozin with metformin, for 15 days, had completed the study thoroughly, with no adverse effects related drop-out patients, lost to follow-up patients or voluntarily withdrawn patients. The combination therapies of 50 mg or 75 mg of remogliflozin and metformin were observed to be safe, which had controlled type II diabetes mellitus among new patients, with significant decrease in the blood sugar levels and the HbA1c levels, within 2 months. There were no adverse effects observed with the combination therapy of 50 mg remogliflozin with metformin as well as the combination therapy of 75 mg remogliflozin with metformin, which were statistically non-significant. The combination therapy of 50 mg remogliflozin with metformin and the combination therapy of 75 mg remogliflozin with metformin were observed to be safe and tolerable.

In several analyses, it was found that gliflozin drugs, the sodium-glucose co-transporter 2 inhibitors, are the newly developed class of oral hypoglycaemic agents used for the treatment of the type-II diabetes mellitus. This drug category was approved by the food and drug administration for the treatment of diabetes, and it has a very unique mechanism of action. The SGLT (sodium-glucose transport) proteins are the macromolecules causing reabsorption of the filtered glucose from the proximal convoluted tubule (PCT) part of the nephron. The significance lies in the fact that these proteins work independent of insulin. Probably the SGLT proteins occur in the nephron and the large intestine. The two main types of SGLT proteins are SGLT 1 and SGLT 2. The SGLT 1 proteins occur in PCT of nephron as well as in the large intestine. The SGLT 2 proteins occur only at PCT part of the nephron. SGLT 1 has a higher affinity but low concentration (with 2:1 sodium-glucose co-transport ratio), thus causing only 10% of total glucose reabsorption; while, SGLT 2 has higher concentration (with 1:1 sodium-glucose co-transport ratio) with 90% of total glucose reabsorption. Selective inhibition of SGLT 2 transport proteins reduces reabsorption rate of glucose molecule resulting in an increase in the glucose excretion rate and reduction in the blood glucose concentration to 40-120 mg/dL, and this is beneficially effective for treating diabetes mellitus type II. The functions (rather than glucose absorption) of SGLT1 in the large intestine is presently under investigation, but it is observed that the inhibition of SGLT1 produces the intestinal complications like diarrhoea, which disturbs the wellness of large intestine. The clinical benefits of SGLT-2 inhibitors are improved glucose control, faster metabolic effect, weight loss, significant reduction in blood pressure, cardiovascular benefits, and reduced sympathetic overactivity. Remogliflozin etabonate (RE), an oral prodrug of remogliflozin, is a selective sodium-glucose co-transporter subtype 2 (SGLT2) inhibitor, having anti-hyperglycemic activity, which is used in the treatment of diabetes mellitus type 2. Remogliflozin etabonate could be an effective oral adjunct to insulin for the treatment of type 1 diabetes. Remogliflozin etabonate has a water solubility of 0.189 mg/ml, and it is a proposed drug for the treatment of non-alcoholic steatohepatitis and type 2 diabetes. Remogliflozin etabonate significantly increases urinary glucose excretion and reduces plasma glucose concentration.[1,5] Remogliflozin is administered in the prodrug form, that is, remogliflozin etabonate (RE) in an immediate release (IR) tablet formulation. Different doses of remogliflozin of 20 mg, 50 mg, 100 mg, 150 mg, 500 mg, and 1000 mg, with varying daily drug intake schedules, are being investigated.[1, 6, 7] After administration, RE is de-esterified by non-specific esterases present in the mucosal cells of the gastrointestinal tract and converted into its active form remogliflozin. RE is rapidly and almost completely absorbed, with an availability in the plasma within 10 minutes with a Tmax of 0.5–1 hour. The administration with standard breakfast slightly delayed the Tmax by approximately 0.5–1.5 hours; without any significant difference in the Cmax or Area under Curve (AUC) relative to the fasting state. Hence RE can be administered with or without food. The plasma protein binding of remogliflozin was around 65%. Either RE or remogliflozin was not preferentially distributed to blood cells, and there was no selective association of RE or its metabolites with melanin containing tissues. In the systemic circulation, remogliflozin is extensively metabolized, leading to N-dealkylation, O-dealkylation, oxidation, loss of glucose, and glucuronidation. *In vitro* studies have demonstrated that the primary enzyme involved in the CYP-based metabolism of remogliflozin is CYP34A, with a minor contribution from CYP2C19. Remogliflozin gets metabolized to two active metabolites, namely: GSK279782 and GSK333081. The major active

metabolite GSK279782 has been shown to account for approximately 16–22% of the concentration of remogliflozin in circulation. The exposure of GSK333081 was found to be extremely low after single-dose studies and hence not considered clinically significant. Remogliflozin has multiple pathways of elimination, like CYP and non-CYP pathways. The mean plasma elimination half-life of remogliflozin and GSK 279782 were around 1.5 to 1.9 hours and 2.3 to 3.8 hours, respectively, in healthy volunteers after a single dose of RE at 100 mg or 250 mg. In the same study, the mean plasma half-life of prodrug was mostly around 0.4 hours to 0.7 hours. Metabolic products of RE are eliminated from the body through renal excretion. In several radio-labelled absorption, metabolic, and excretion (AME) studies, approximately 93% was excreted in the urine, with 11% of the dose being recovered as remogliflozin in urine; and the majority of drug-related material is eliminated via the urine as inactive glucuronide metabolites. On the evaluation of the inhibitory concentration of remogliflozin, it was demonstrated that Ki values were 12.4 and 4520 nmol/l for SGLT2 and SGLT1, respectively. This shows that remogliflozin is a selective inhibitor of SGLT2.[1, 2] The adverse effects of SGLT2 inhibitor drugs include diabetic ketoacidosis, bone fracture, urinary tract infection, genital fungal infection, foot and toe amputation, breast cancer, Leydig cell tumour and bladder cancer.[1, 5] A single dose, dose-escalation study in healthy human volunteers, and T2DM patients observed 24-hour urine glucose excretion (UGE) to be 17.5–40.5g and 66.6 to 112.6g, respectively, in a dose-dependent manner. The UGE showed a dose-dependent increase in total urine glucose excretion (UGE) from 0 to 24 hours in fasted and fed conditions. However, UGE increased less proportionally with an increase in dose from 150 mg to 500 mg, indicating a plateau effect, as observed with drugs of this class. Urinary glucose excretion was higher in patients with T2DM than in volunteers because of higher plasma glucose concentrations in patients. On correcting the UGE according to circulating plasma glucose concentrations and creatinine clearance, to estimate the percentage filtered glucose load, it was found to be similar in both healthy individuals as well as T2DM patients. Clinically significant increase in UGE and urine volumes were observed in 12-week dose-ranging (50–1000 mg) study in drug naïve T2DM patients. A dose ordered increase at 12 weeks from baseline was observed in UGE over 24 hours ranging from 61 to 96 g/ day. A similar dose-ordered increase at 12 weeks in urine volume was observed (~0.5L/day). The key pharmacokinetic and pharmacodynamic studies that assisted the characterization of clinical profiles were also significant.[1,2]

Therefore, this study suffices its objective, amply analysing the pharmacotherapeutic prescription patterns and assessing the occurrence of adverse drug reactions with 50 mg or 75 mg remogliflozin with 500 mg metformin combination treatment, in global tertiary care hospitals, in type II diabetes mellitus patients. This type of stepwise increase in a single drug dose within a combination therapy potentiates the effective evidence-based selective pharmacotherapeutic response of the diabetic patients to gradual modification of the combination regimens; thereby also focussing on the minimalization of adverse effects of anti-diabetic drugs along with effective clinical responses, shown even with lowered doses of a single drug in the prescribed combination drug regimens. There were no limitations in this study.

This study would remain a significant landmark towards the determination of precisely adjusted dose schedules of anti-diabetic singular drug regimen or combination drug regimens, each dose being specifically titrated in accordance with the investigative and evidence-based pharmacotherapeutic effectiveness and clinical response of the diabetic patient, emphasised further by the significant authentication of drug efficacy and safety.

CONCLUSIONS

This study established that the prescription rates of anti-diabetic percentage glycaemic stabilisation were as follows: prescription percentage of well-controlled glycaemic stabilisation with metformin combination therapies > prescription percentage of inadequate glycaemic stabilisation with metformin combination therapies. It also established that the prescription content analyses showed 100% completeness, with significant pharmacotherapeutic molecular efficacy. The combination therapies consisting of the increasing doses of remogliflozin 50 mg or 75 mg, along with 500 mg metformin, were safe and tolerable. This study would remain a significant landmark towards the determination of precisely adjusted dose schedules of anti-diabetic singular drug regimen or combination drug regimens, each dose being specifically titrated in accordance with the investigative and evidence-based pharmacotherapeutic effectiveness and clinical response of the diabetic patient, emphasised further by the significant authentication of drug efficacy and safety.

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