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Original Article

A Pharmacovigilance Study of the Combination Therapies of Augmenting Drug Doses of 50 mg and 75 mg Remogliflozin with 500 mg Metformin among Type II Diabetics, Along Global Pharmacoepidemiology: An Appraisal of Rational Pharmacotherapeutics in Metabolic Medicine

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Abstract

Introduction: Diabetes mellitus type II is globally very common, yet neglected. Remogliflozin, a selective insulin-independent sodium glucose cotransporter subtype 2 inhibitor, inhibits reabsorption of renal glucose, lowers blood sugar, and causes glucosuria, in type II diabetes mellitus patients. Metformin, as a combination antidiabetic drug, lowers serum glucose levels, by the activation of 5' adenosine monophosphate-activated protein kinase.

Objectives: The objectives of this endocrinological rational pharmacotherapeutic study were the safety evaluation of augmenting doses in the combination therapies of 50 mg and then 75 mg remogliflozin with 500 mg metformin, in type II diabetes mellitus patients, in tertiary care medical college hospitals, along a global pharmacoepidemiological perspective.

Methods: A total of 150 new early moderate grade type II diabetes mellitus patients were prescribed oral metformin 500 mg once daily for 30 days. Then, diabetics uncontrolled with metformin 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 safety assessment, along with blood sugar and hemoglobin A1c levels and urine routine examination, on day 0, day 30, day 46, day 60, and further follow-up, was recorded and statistically analyzed.

Results: The adverse effects with the combination therapy of 50 mg remogliflozin with 500 mg metformin and then the combination therapy of 75 mg remogliflozin with 500 mg metformin were statistically non-significant; hence, both were safe and tolerable.

Conclusions: The combination therapy of 50 mg remogliflozin and 500 mg metformin and, then, the combination therapy of 75 mg remogliflozin and 500 mg metformin, were safe and tolerable.

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Key words: Biguanides, Metformin, Sodium glucose cotransporter subtype 2 inhibitors, Remogliflozin, Pharmacovigilance, Augmenting drug doses in combination therapies, Diabetology and metabolic medicine

INTRODUCTION

Diabetes mellitus type II is one of the most common, yet often neglected disease, that the world has witnessed in the recent times. The global incidence and prevalence of type 2 diabetes mellitus (T2DM) is on a perennial increase, with about one in 11 adults having diabetes mellitus and 90% among them being type 2 diabetic. According to the International Diabetes Federation, 425 million global population has diabetes mellitus, accounting for two-thirds of adults aged 20–64 years, and the proportion of deaths due to diabetes mellitus before the age of 60 years ranges from 36 to 73%. Diabetes mellitus has its highest prevalence in 10 countries, with almost 60% of the global disease burden, mostly distributed in China (114 million people), India (73 million people), and the USA (30 million people). Given its extensive occurrence, the management of diabetes mellitus through effective treatment interventions is of utmost significance in the field of clinical research.[1,2]

The diagnostic criteria of type II diabetes mellitus by the American Diabetes Association (ADA) include the following:

1. A fasting plasma glucose level of 126 mg/dl (7.0 mmol/L) or higher, or
2. A 2 h plasma glucose level of 200 mg/dl (11.1 mmol/L) or higher during a 75 g oral glucose tolerance test, or
3. A random plasma glucose of 200 mg/dl (11.1 mmol/L) or higher in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, or
4. A hemoglobin A1c (HbA1c) level of 6.5% (48 mmol/mol) or higher.[1,3]

With remogliflozin, a selective insulin-independent sodium glucose cotransporter subtype 2 (SGLT2) inhibitor, the management of type II diabetes mellitus has taken a quantum leap, producing antihyperglycemic 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 glycemic control, significant improvements in HbA1c, insulin sensitivity and β-cell function, weight loss, blood pressure reduction, cardiovascular and renal protection by significantly increasing high-density lipoprotein cholesterol, decreasing low-density lipoprotein cholesterol, reducing albuminuria, and delaying the progression of nephropathy. The ADA and the European Association for the Study of Diabetes suggest the therapeutic use of SGLT2 inhibitors for patients with diabetic comorbidities such as cardiovascular disease (including heart failure and atherosclerotic cardiovascular disease) and chronic kidney disease.[1,4]

Metformin has considerable improved outcomes, as a combination antidiabetic 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 (e.g., 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) AMPK. 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.[1,5,6]

The American Association of Clinical Endocrinologists guidelines for T2DM management suggest lifestyle therapy, medically assisted weight loss, and individual goals of achieving HbA1c level of ≤6.5%. The determining factors behind the choice of antidiabetic drugs are the different patient characteristics, such as glycemic index, weight, lifestyle, comorbidities, and undesirable side effects of pharmacotherapeutic management. The commonly associated side effects with oral antidiabetic agents are hypoglycemia, weight gain due to hyperinsulinemia, gastrointestinal symptoms, and hepatorenal toxicity. The critical effects under consideration for the clinical rationale of the antidiabetic drugs are their potential for hypoglycemia, 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 antidiabetic combination therapies, with the augmenting doses of remogliflozin: 50 mg remogliflozin and 500 mg metformin, which were 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, hypoglycemia risk, impact on weight, cost, risk for side effects, and patient preferences were also taken into consideration.[1,4-6]

Objectives

The objectives of this endocrinological rational pharmacotherapeutic study were the safety evaluation of the combination therapies of augmenting drug doses of 50 mg and then 75 mg remogliflozin with 500 mg metformin, in type II diabetes mellitus patients, in tertiary care medical college hospitals, along a global pharmacoepidemiological perspective.

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 the 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 in compliance with the global regulatory requirements. An informed consent was obtained from each patient.

Selection Criteria of the Study Participants

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 ADA diagnosis criteria, (vi) cooperative 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 antidiabetic drug, and (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 comorbidities, (vi) cardiac, renal, or any other associated complications or comorbidities, (vii) any chronic disease intervening with the study data, (x) pregnant or lactating women, (xi) pediatric or geriatric patients, (xii) other associated medical illness or disorders, like urogenital tract infections, having impact on study results, and (xiii) female patients using hormonal contraceptives.

Study design

This was a global, multicenter, prospective, randomized, open-labeled study.

Study population

The study population was 150 new type II diabetes mellitus patients, of early moderate grade.

Place of study

The place of research study and the compilation of the study literature 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 Mamata Medical College and Hospitals, Rama Medical College Hospital and Research Centre, Rama University, Dr. Moumita Hazra's Polyclinic and Diagnostic Centre, Hazra Nursing Home, Shri Ramkrishna Institute of Medical Sciences and Sanaka Hospitals, Hi-Tech Medical College and Hospital, K.D. Medical College Hospital and Research Center, Gouri Devi Institute of Medical Sciences and Hospital, J.J.M. Medical College and Hospitals, GIOSTAR IRM Institutes, Hospitals and Laboratories, and Mahuya Diagnostic Centre and Doctors' Chambers.

Study period

The study period, including the research study and the compilation of the study literature, was 5 months: June 2015 and from July 2021 to December 2021.

Study procedure

A total of 150 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 150 patients, 50 diabetic patients uncontrolled with metformin, (i) who had achieved adequate glycemic 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 100 patients 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 patients' characteristics, diabetic symptoms assessment, patients' disease, and disease-related history were recorded with a pro forma. 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 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 safety assessment was done with an Adverse Event Case Report Form, by the monitoring of adverse drug reactions, such as hypoglycemia, weakness, gastrointestinal disturbances, abdominal pain, and upper respiratory tract infections, after metformin monotherapy, from day 0 to day 30. Then, the safety was assessed by monitoring any adverse reaction, such as genital mycotic infections, urinary tract infections, pyrexia, headache, dizziness, nausea, gastrointestinal disturbances, hypoglycemia, 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 analyzed by Z-test, and test of significance with *P* values, with subsequent tabular representations.

RESULTS

The demographic characteristics of the patients, in this study, were comparable. Among 150 new type II diabetes mellitus patients, of early moderate grade, receiving metformin monotherapy for 1 month, 50 uncontrolled diabetic patients, (i) who had achieved adequate glycemic 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 100 patients 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 dropout 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 1 depicts the occurrence of adverse effects with 50 mg remogliflozin and 500 mg metformin combination therapy. Table 2 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 500 mg metformin and then, with the combination therapy of 75 mg remogliflozin with 500 mg metformin, which were statistically non-significant. The combination therapy of 50 mg remogliflozin with 500 mg metformin and, then, the combination therapy of 75 mg remogliflozin with 500 mg metformin were observed to be safe and tolerable.

DISCUSSION

Gliflozin drugs, the sodium-glucose cotransporter 2 inhibitors, are the newly developed class of oral

Table 1: The occurrence of adverse effects with 50 mg remogliflozin and 500 mg metformin combination therapy

Adverse effects	Number of patient occurrence	Z value	*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 2: The occurrence of adverse effects with 75 mg remogliflozin and 500 mg metformin combination therapy

Adverse effects	Number of patient occurrence	Z value	*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

hypoglycemic 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 sodium-glucose transport (SGLT) 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 cotransport ratio), thus causing only 10% of total glucose reabsorption; while, SGLT 2 has higher concentration (with 1:1 sodium-glucose cotransport 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 are presently under investigation, but it is observed that the inhibition of SGLT1 produces the intestinal complications like diarrhea, 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 SGLT2 inhibitor, having antihyperglycemic activity, which is used in the treatment of diabetes mellitus type 2. RE could be an effective oral adjunct to insulin for the treatment of type 1 diabetes. RE 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. RE significantly increases urinary glucose excretion and reduces plasma glucose concentration.[1,7]

Remogliflozin is administered in the prodrug form, that is, 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.[1,8,9] 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 min with a Tmax of 0.5–1 h. The administration with standard breakfast slightly delayed the Tmax by approximately 0.5–1.5 h; without any significant difference in the Cmax or area under curve 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, such as CYP and non-CYP pathways. The mean plasma elimination half-life of remogliflozin and GSK 279782 were around 1.5–1.9 h and 2.3–3.8 h, 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 0.4–0.7 h. Metabolic products of RE are eliminated from the body through renal excretion. In several radiolabeled absorption, metabolic, and excretion 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 through 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.[1,4]

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 tumor, and bladder cancer.[1,7]

In this study, among 150 new type II diabetes mellitus patients, of early moderate grade, receiving metformin monotherapy for 1 month, 50 uncontrolled diabetic patients, (i) who had achieved adequate glycemic 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 100 patients received 50 mg remogliflozin with 500 mg metformin combination therapy, for 15 days, and subsequently 75 mg remogliflozin with 500 mg metformin combination therapy, for 15 days. These patients had completed the study thoroughly, with no adverse effects related dropout patients, lost to follow-up patients, or voluntarily withdrawn patients. The demographic characteristics of the patients were comparable. The combination therapies of increasing doses of remogliflozin and metformin were observed to be safe, and they have controlled type II diabetes mellitus among new patients, with significant decrease in the blood sugar levels and the HbA1c levels, within 2 months. This supports the successful synergistic effect of these antidiabetic combination therapies, with a gradually increasing dose of remogliflozin. There were no adverse effects observed with the augmenting doses of combination therapies of 50 mg and then 75 mg of remogliflozin with 500 mg metformin, which were statistically non-significant. The combination therapies of 50 mg and then 75 mg remogliflozin with 500 mg metformin were observed to be safe and tolerable. The results showed a significant decrease in the occurrence of adverse effects associated with these combination therapies, which were quite beneficial in the treatment of diabetes mellitus type II patients.

A single-dose, dose-escalation study in healthy human volunteers and T2DM patients observed 24 h urine glucose excretion (UGE) to be 17.5–40.5 g and 66.6–112.6 g, respectively, in a dose-dependent manner. The UGE showed a dose-dependent increase in total UGE from 0 to 24 h 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 and T2DM patients. Clinically significant increase in UGE and urine volumes was 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 h ranging from 61 to 96 g/day. A similar dose-ordered increase at 12 weeks in urine volume was observed (~0.5 L/day). The key pharmacokinetic and pharmacodynamic studies that assisted the characterization of clinical profiles were also significant.[1,4]

Therefore, this study suffices its objective, amply assessing the globally relevant prescribing rationale of pharmacotherapeutic application in molecular medicine, along with the safety evaluation of the antidiabetic combination therapies with subsequent increase in drug doses of 50 mg, and then, 75 mg remogliflozin with 500 mg metformin, in type II diabetes mellitus patients, in tertiary care medical college hospitals. 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 focusing on the minimization of adverse effects of antidiabetic drugs along with effective clinical responses, shown even with lowered doses of a single drug in the prescribed combination drug regimens.

CONCLUSIONS

This study established that the combination therapies consisting of the increasing doses of remogliflozin 50 mg and then 75 mg, along with 500 mg metformin, were safe and tolerable. This study would remain a significant landmark toward the determination of precisely adjusted dose schedules of antidiabetic 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, emphasized further by the significant authentication of drug efficacy and safety.

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