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AN ENDOCRINOLOGICAL PHARMACOVIGILANCE STUDY ON THE SAFETY ASSESSMENT OF METFORMIN MONOTHERAPY AND THE COMBINATION THERAPY OF REMOGLIFLOZIN WITH METFORMIN, IN THE NEW TYPE II DIABETES MELLITUS PATIENTS, IN TERTIARY CARE MEDICAL COLLEGE HOSPITALS

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ABSTRACT

Introduction: Diabetes mellitus type II is globally very common, yet neglected. 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, has similar improved outcomes, as a combination anti-diabetic drug, lowering serum glucose levels, by the activation of 5' adenosine monophosphate (AMP) activated protein kinase. **Objective:** An endocrinological pharmacovigilance study on the safety assessment of metformin monotherapy and the combination therapy of remogliflozin with metformin, in the new type II diabetes mellitus patients, in tertiary care medical college hospitals. **Methods:** 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. The safety assessment, along with blood sugar and HbA1c levels and urine routine examination, on day 0, day 30, and day 46, were recorded and statistically analysed. **Results:** The adverse effects with metformin monotherapy and the combination therapy of remogliflozin with metformin were statistically non-significant; hence both were safe and tolerable. **Conclusions:** The monotherapy of

metformin and the combination therapy of remogliflozin and metformin were safe and tolerable.

KEYWORDS: Remogliflozin, Sodium glucose co-transporter subtype 2 inhibitors, Metformin, Biguanides, Diabetes mellitus type II.

INTRODUCTION

Diabetes mellitus type II is one of the universally prevalent common, yet often neglected, disease, that the world has witnessed in the recent times. The incidence and prevalence of type 2 diabetes mellitus (T2DM) are increasing globally, with about one in 11 adults having diabetes mellitus and 90% of them having T2DM. According to the International Diabetes Federation, 425 million people worldwide have 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%. The ten countries with the highest prevalence of diabetes mellitus account for almost 60% of the global disease burden, with China (114 million people), India (73 million people), and the USA (30 million people) contributing to most of this. Therefore, the management of diabetes mellitus through effective treatment interventions is of the utmost importance in the field of clinical research.[1] The American Association of Clinical Endocrinologists (AACE) provides guidelines for T2DM management, which include lifestyle therapy, medically assisted weight loss, and individual goals of achieving haemoglobin $A1_C$ ($HbA1_C$) level of $\leq 6.5\%$. The patient characteristics, like glycemic index and weight, lifestyle, co-morbidities, and undesirable side effects of pharmaco-therapeutic management, determine the choice of antidiabetic agents. The commonly associated side effects with oral anti-diabetic agents are hypoglycemia, weight gain due to hyperinsulinemia, gastrointestinal symptoms, and hepato-renal toxicity. The increase in adverse effects demands a safer antidiabetic agent. The critical effects under consideration are the drug's potential for hypoglycemia, weight gain, and long term side effects.

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 the diabetes mellitus type II, and also in insulin resistant patients, when given in monotherapy or in combination with metformin. Remogliflozin inhibits reabsorption of glucose in the kidney, thus lowering blood sugar, and causing glucosuria. Clinical guidelines recommend the SGLT2 inhibitors as one of the

pharmacological approaches for second-line therapy, 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 significant 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 using SGLT2 inhibitors for patients with diabetic co-morbidities like cardiovascular disease (including heart failure, and atherosclerotic cardiovascular disease) and, chronic kidney disease.[2]

Metformin, has similar improved outcomes, as a combination anti-diabetic drug, overcoming insulin resistance and lowering serum glucose levels, by the activation of 5' adenosine monophosphate (AMP) activated protein kinase. Metformin is effective and safe, is inexpensive, and may reduce risk of cardiovascular events and death. It has beneficial effects on $HbA1_C$ and weight.[3]

Diagnostic Criteria of type II diabetes mellitus by American Diabetes Association include the following.

1. A fasting plasma glucose (FPG) level of 126 mg/dl (7.0 mmol/L) or higher, or.
2. A 2-hour plasma glucose level of 200 mg/dl (11.1 mmol/L) or higher during a 75-g oral glucose tolerance test (OGTT), 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 haemoglobin A1c (HbA1c) level of 6.5% (48 mmol/mol), or higher.[4]

A patient-centered approach should be used to guide the choice of pharmacologic agents. Considerations include effect on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, cost, risk for side effects, and patient preferences.[3]

OBJECTIVE

The objective was an endocrinological pharmacovigilance study on the safety assessment of metformin monotherapy and the combination therapy of remogliflozin with metformin, in the new type II diabetes mellitus patients, in tertiary care medical college hospitals.

MATERIALS AND 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 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 presenting with new type II diabetes mellitus, of early moderate grade, (iv) type II diabetes mellitus American Diabetes Association diagnosis criteria, (v) co-operative and conscious patients, (vi) patients willing to undergo all pre and post- treatment investigations and willing to complete the entire course of treatment, (vii) patients who have given consent and are willing to go for a follow-up, (viii) patients not taking any previous anti-diabetic drug, (ix) 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 multi-centre, prospective, randomized, open-labelled study.

Study Population

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

Study Period

The study period was 1.5 months, from October, 2020 to December, 2020.

Place of Study

The place of research study and the compilation of the study litaerature were the Departments of Pharmacology, Clinical Pharmacology, Pharmacovigilance, Molecular Pharmacology, Endocrinological Pharmacology, Rational Pharmacotherapeutics, Pathology, and Clinical Pathology, in Rama Medical College Hospital and Research Centre, Uttar Pradesh, India and J.J.M. Medical College and Hospital, Karnataka, India.

Study Procedure

150 new type II diabetes mellitus patients, of early moderate grade, were prescribed oral metformin 500 mg 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 remogliflozin once daily and 500 mg metformin once daily, for 15 days.

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 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 either of the combination therapies at day 46, and (d) further follow-up.

The safety assessment was done by the monitoring of adverse drug reactions, like 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, like 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 and 500 mg metformin once daily, from (i) day 30 to day 46, and (ii) further follow-up.

Statistical Analysis

At the study completion point, the observations recorded in this study, were statistically analysed by Z Test, and Test of significance with p values.

RESULTS

The demographic characteristics of the patients 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 the study. The remaining 100 patients, received remogliflozin and metformin combination therapy, 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 monotherapy of metformin and the combination therapy 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, in 1.5 months.

Table 1: The Occurrence of Adverse Effects With Metformin Monotherapy.

Adverse effects	Number of patient occurrence	Z value	p value
Hypoglycemia	0	-	non-significant
Weakness	0	-	non-significant
Gastrointestinal disturbances	0	-	non-significant
Abdominal pain	0	-	non-significant
Upper respiratory tract infections	0	-	non-significant

Table 2: The Occurrence Of Adverse Effects With Metformin And Remogliflozin 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	0	-	non-significant

disturbances			
Hypoglycemia	0	-	non-significant
Weakness	0	-	non-significant
Abdominal pain	0	-	non-significant

Table 1 depicts the occurrence of adverse effects with metformin monotherapy. Table 2 depicts the occurrence of adverse effects with metformin and remogliflozin combination therapy.

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

DISCUSSION

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 remogliflozin and metformin combination therapy, 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 demographic characteristics of the patients were comparable. The monotherapy of metformin and the combination therapy 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, in 1.5 months. There were no adverse effects observed with the monotherapy of metformin as well as the combination therapy of remogliflozin and metformin, which were statistically non-significant. The monotherapy of metformin and the combination therapy of remogliflozin and metformin were observed to be safe and tolerable.

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 class approved by food and drug administration for the treatment of diabetes, has a unique mechanism of action. The SGLT (sodium-glucose transport) proteins are the macromolecules which cause reabsorption of the filtered glucose from the proximal convoluted tubule (PCT)

part of the nephron, and most important part is that these proteins work independently of insulin. Probably the SGLT proteins occur in the nephron and the large intestine. There are two main types of SGLT proteins known as SGLT 1 and SGLT 2. The SGLT1 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), and thus, they bring about only the 10% of total glucose reabsorption, on the other hand, the SGLT 2 has higher concentration (with 1:1 sodium-glucose co-transport ratio) and shows the 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, with a beneficial effect for treating diabetes mellitus type II. The functions (rather than glucose absorption) of SGLT1 in the large intestine is still unknown, but it is observed that the inhibition of SGLT1 produces the intestinal complications like diarrhoea, which disturbs the wellness of large intestine.

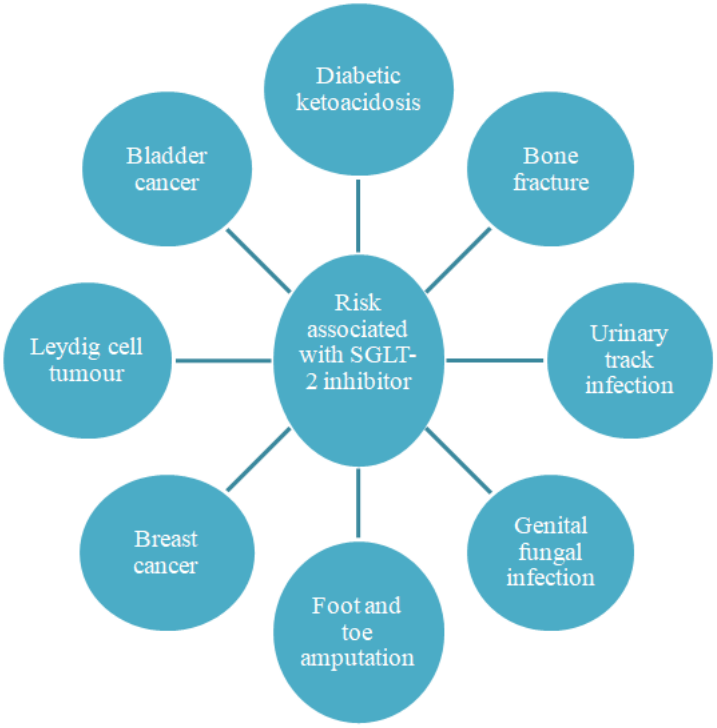
The benefits of SGLT-2 inhibitors are improved glucose control, faster metabolic effect, weight loss, significant reduction in blood pressure, cardiovascular benefits, and reduced sympathetic overactivity.

Remogliflozin Etabonate is an orally available prodrug of remogliflozin. It 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 etabonates 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. Remogliflozin 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.[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.[6, 7] After administration, RE is de-esterified by non-specific esterases present in the mucosal cells of the gastrointestinal tract to get converted into its active form remogliflozin. RE is rapidly and almost completely absorbed and available 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; however, there was no 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, which are CYP as well as 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 radio-labelled absorption, metabolic, and excretion (AME) studies, approximately 93% was excreted in the urine, of which about 11% of the dose was recovered as remogliflozin in urine; the majority of drug-related material is eliminated via the urine as inactive glucuronide metabolites. The inhibitory concentration of remogliflozin was evaluated, and Ki values of 12.4 and 4520 nmol/l for SGLT2 and SGLT1, respectively, were demonstrated. This shows that remogliflozin is a selective inhibitor of SGLT2. 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.[2]



Risk Associated with SGLT2 Inhibitors[5]

CONCLUSIONS

This study established that the monotherapy of metformin and the combination therapy of remogliflozin and metformin were safe and tolerable.

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