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Original Article

A Study of the Usual Clinical Pharmacological Prescription Patterns of Metformin, Sitagliptin, and Remogliflozin among the Early Moderate Grade New Type II Diabetes Mellitus Patients in Tertiary Care Hospitals

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Abstract

Introduction: Remogliflozin, a selective insulin-independent sodium glucose cotransporter subtype 2 (SGLT2) inhibitor, inhibits reabsorption of renal glucose, lowers blood sugar, and causes glucosuria, in type II diabetes mellitus (T2DM) patients. Inhibition of dipeptidyl peptidase-4 (DPP-4) inhibitors enhances hormonal activity of incretins (glucagon-like peptide-1, glucose-dependent insulinotropic polypeptide, and gastrin-releasing peptide), stimulates insulin release, and reduces glucagon secretion, thus producing anti-hyperglycemic activity in T2DM patients.

Objective: The objective of this study was to assess the usual clinical pharmacological prescription patterns of metformin, sitagliptin, and remogliflozin among the early moderate grade new T2DM patients in tertiary care hospitals.

Materials and Methods: A total of 150 new early moderate grade T2DM patients were prescribed oral metformin 500 mg once daily, sitagliptin 25 mg once daily, or remogliflozin 50 mg once daily for 1.5 months, in monotherapy, or in combination therapy, or in a mixed regimen of monotherapy and combination therapy. The safety and efficacy assessments, with blood sugar and hemoglobin A1C levels and urine routine examination, at subsequent intervals and follow-up, were recorded and statistically analyzed. The number of prescriptions for each drug was recorded, and the corresponding prescription rates were statistically analyzed in percentages.

Results: Metformin was most commonly prescribed (120 prescriptions, 80%) followed by sitagliptin (21 prescriptions, 14%) and remogliflozin (9 prescriptions, 6%).

Conclusions: Prescription frequency of metformin was followed by sitagliptin and then by remogliflozin.

Key words: Biguanides, Metformin, Dipeptidyl peptidase-4 inhibitor, Sitagliptin, Sodium glucose cotransporter subtype 2 inhibitor, Remogliflozin

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INTRODUCTION

Diabetes mellitus type II is a common, but often neglected disease, that the world has witnessed in the recent times. The American Association of Clinical Endocrinologists (AACE) provides guidelines for type-2 diabetes mellitus (T2DM) management, which include lifestyle therapy,

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medically assisted weight loss, and individual goals of achieving hemoglobin A1C (HbA1C) level of ≤6.5%. The patient characteristics, such as glycemic index and weight, lifestyle, comorbidities, and undesirable side effects of pharmacotherapeutic management, determine the choice of antidiabetic agents. The commonly associated side effects with oral antidiabetic agents are hypoglycemia, weight gain due to hyperinsulinemia, gastrointestinal symptoms, and hepatorenal 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.

Remogliflozin, a selective insulin-independent sodium glucose cotransporter subtype 2 (SGLT2) inhibitor, 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 such as adequate glycemic control, significant improvements in HbA1C, 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 comorbidities such as cardiovascular disease (including heart failure and atherosclerotic cardiovascular disease) and chronic kidney disease.[1,2]

Inhibition of dipeptidyl peptidase-4 (DPP-4) inhibitors enhances the hormone activity of incretins, such as glucagon-like peptide-1 (GLP-1) and other bioactive peptides (glucose-dependent insulinotropic polypeptide [GIP] and gastrin-releasing peptide), thus stimulating the release of insulin and reducing the secretion of glucagon, when given in monotherapy or in combination with metformin. This effect decreases the blood glucose levels as well as HbA1c levels in T2DM patients, without causing severe hypoglycemia.[3,4]

Metformin has similar improved outcomes, as a monotherapeutic as well as a combination antidiabetic 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 HbA1C and weight.[5]

Objective

The objective is a study of the usual clinical pharmacological prescription patterns of metformin, sitagliptin, and remogliflozin among the early moderate grade new T2DM patients in tertiary care 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 T2DM, of early moderate grade, (iv) T2DM ADA diagnosis criteria, (v) cooperative 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 antidiabetic drug, and (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 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, having impact on study results, and (xiii) female patients using hormonal contraceptives.

Study Design

A global, multicenter, retrospective, observational, and analytical study of the clinical prescriptions was performed.

Study Population

The study population consisted of 150 treated new T2DM patients, of early moderate grade.

Study Period

The study period, comprising the periods for the research study and the compilation of the study literature, was 1.5 months, from June 2021 to August 2021.

Place of Study

The research study and the compilation of the study literature were done in the Departments of Pharmacology, Clinical Pharmacology, Pharmacovigilance, Internal Medicine, Endocrinology, Pathology, and Clinical Pathology, in Dr. Moumita Hazra's Polyclinic and Diagnostic Centre, Hazra Nursing Home, Rama Medical College Hospital and Research Centre, J.J.M. Medical College and Hospital, and Shri Ramkrishna Institute of Medical Sciences and Sanaka Hospitals.

Study Procedure

A total of 150 new early moderate grade T2DM patients were prescribed oral metformin 500 mg once daily, sitagliptin 25 mg once daily, or remogliflozin 50 mg once daily, for 1.5 months, in monotherapy, or in combination therapy, or in a mixed regimen of monotherapy and combination therapy.

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 postprandial blood sugar level, HbA1c level, and urine routine examination findings including sugar and albumin levels and microscopy, at subsequent intervals, and follow-up.

The safety assessment was done by the monitoring of adverse drug reactions, at subsequent intervals, and follow-up.

The usual prescription patterns of all three drugs were analyzed. The number of prescriptions of 150 patients treated with each drug: Metformin, sitagliptin, and remogliflozin were recorded; and the percentage of prescriptions for each drug was calculated.

Statistical Analysis

The corresponding prescription rates were statistically analyzed in percentages.

RESULTS

The demographic characteristics of the patients were comparable.

Figure 1 depicts that metformin was most commonly prescribed (120 prescriptions, 80%) followed by sitagliptin (21 prescriptions, 14%) and remogliflozin (9 prescriptions, 6%).

The prescription rates of antidiabetic drugs were as follows: Metformin > sitagliptin > remogliflozin.

The monotherapy, or combination therapy, or mixed regimen of monotherapy and combination therapy of metformin, sitagliptin, or gemigliptin, was observed to be quite efficacious, which had controlled T2DM among new patients, with significant decrease in the blood sugar levels and the HbA1c levels, in the successive 3 months. The adverse effects observed with monotherapy, or combination therapy, or mixed regimen of monotherapy and combination therapy, were statistically non-significant. Therefore, the monotherapy, or combination therapy, or mixed regimen of monotherapy and combination therapy, was safe and tolerable.

DISCUSSION

Gliflozin drugs, the sodium-glucose cotransporter 2 inhibitors, are the newly developed class of oral hypoglycemic agents used for the treatment of the T2DM. This class approved by food and drug administration for the treatment of diabetes, has a unique mechanism of action. The 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 cotransport 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 cotransport ratio) and shows 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 are still unknown, but it is observed that the inhibition of SGLT1 produces the intestinal complications like diarrhea, 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.[6]

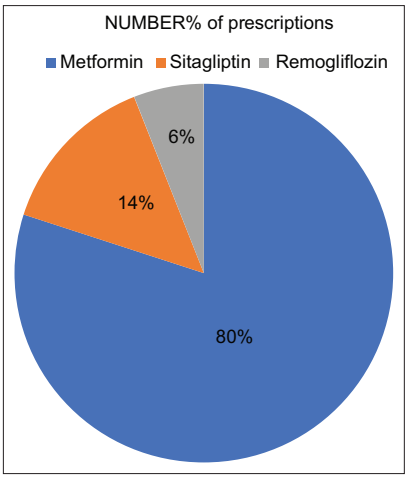

Figure 1: The prescription rates of different antidiabetic drugs in percentages

Anti-DPP-4 antihyperglycemic agents have been widely used for patients with T2DM under guidelines of diabetes associations and proved to be effective in the enhancement of beta-cell function through ameliorating serum incretin hormone concentrations (two major incretins, GLP-1 and GIP) – an anti-beta-cell apoptosis agent. There have been two incretin-related therapies for patients with T2D, namely, GLP-1 agonists, exedin-4, and DPP-4 inhibitor, sitagliptin. In 2009, the AACE/ACE issued the guideline for antihyperglycemic treatment protocol which mentioned about the usage of incretin therapies as the first-line drug for newly diagnosed patients with T2D (i.e., incretin therapies could be monotherapy or in combination with other antidiabetic drugs such as biguanide, sulfonylurea, or insulin). These days, incretin therapies regarding treatment for patients with T2D, have been developed on a global scale and shown positive effects on not only glycemic control but prevention from chronic diabetic complications as well. While anti-DPP4 agents have many effects on antihyperglycemic conditions, there have been little researches on the Asian population to investigate the role of these drugs on beta-cell function, peripheral insulin sensitivity, insulin resistance, and serum GLP-1 concentrations in comparison to healthy subjects but results were controversial.[3]

In this study, the demographic characteristics of the patients were comparable. Metformin was most commonly prescribed (120 prescriptions, 80%) followed by sitagliptin (21 prescriptions, 14%) and remogliflozin (9 prescriptions, 6%), as depicted in Figure 1. The prescription rates of anti-diabetic drugs were as follows: Metformin >sitagliptin >remogliflozin.

The monotherapy, or combination therapy, or mixed regimen of monotherapy and combination therapy of metformin, sitagliptin, or gemigliptin, was observed to be quite efficacious, which had controlled T2DM among new patients, with significant decrease in the blood sugar levels and the HbA1c levels, in the successive 3 months. The adverse effects observed with monotherapy, or combination therapy, or mixed regimen of monotherapy and combination therapy, were statistically non-significant. Therefore, the monotherapy, or combination therapy, or mixed regimen of monotherapy and combination therapy, was safe and tolerable.

CONCLUSIONS

The prescription frequency of metformin was followed by sitagliptin and then by remogliflozin.

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