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Original Research Article

A Clinical Pharmacological Study on the Prevailing Prescription Patterns Appraisal of the Combination Therapies of Metformin and Remogliflozin, Metformin and Sitagliptin, and Metformin and Gemigliptin, among Early Grade Type II Diabetic Patients

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Abstract

Background: Oral hypoglycemic response is brought about through the activation of 5' adenosine monophosphate induced protein kinase by metformin, inhibition of dipeptidyl peptidase-4 by the dipeptidyl peptidase-4 inhibitors, sitagliptin and gemigliptin, and the inhibition of a selective insulin-independent sodium glucose cotransporter subtype 2 by remogliflozin.

Objectives: The objective of this clinical pharmacological study is the prevailing prescription patterns appraisal of the combination therapies of metformin and remogliflozin, metformin and sitagliptin, and metformin and gemigliptin, among early grade type II diabetic patients.

Materials and Methods: 93 early moderate grade, type II diabetes mellitus patients, were prescribed oral 250 mg metformin and 50 mg remogliflozin combination therapy, or oral 250 mg metformin and 25 mg sitagliptin combination therapy, or 250 mg metformin and 25 mg gemigliptin combination therapy, once daily, for 3 months. The prescription patterns of the administered anti-diabetic combination therapies, and the prescription content were analysed, and statistically interpreted.

Results: Among the prescribed anti-diabetic combination therapies, metformin and sitagliptin was most commonly prescribed (67 prescriptions, 72.04%), followed by metformin and remogliflozin, which was followed by metformin and gemigliptin. The completeness of the different aspects of the prescription contents was 100%.

Conclusions: Metformin and sitagliptin was the most commonly prescribed anti-diabetic combination therapy, followed by metformin and remogliflozin, and metformin and gemigliptin. The prescriptions had 100% completeness.

Keywords: Biguanides, Metformin, Dipeptidyl peptidase-4 inhibitors, Sitagliptin, Gemigliptin, Sodium glucose co-transporter subtype-2 inhibitors, Remogliflozin, Anti-diabetic combination treatment prescription appraisal.

Introduction

The global diagnostic criteria and anti-hyperglycaemic treatment protocol, as described or laid down by the American Diabetes Association, American Association of Clinical Endocrinologists, American College of Endocrinology

(2009), European Association for the Study of Diabetes, and International Diabetes Federation, have stated quite beneficial anti-diabetic diagnostic and combination pharmacotherapeutic details.

Metformin overwhelms the insulin resistance and lowers serum glucose levels, by activating 5' adenosine monophosphate (AMP) induced protein kinase. It also causes significant HbA1c and weight reduction, along with decrease in cardiovascular co-morbidities and mortalities.

Dipeptidyl peptidase-4 inhibitors, like sitagliptin and gemigliptin, inhibit dipeptidyl peptidase-4, and hence enhance the endocrinological functions of incretins. Thus, in monotherapeutic or combination therapeutic regimens with metformin, these stimulate insulin release, reduce glucagon secretion, decrease blood glucose levels and HbA1c levels, among type II diabetic patients, without causing severe hypoglycaemia.

Remogliflozin, a selective insulin-independent sodium glucose cotransporter subtype 2 inhibitor, inhibits renal glucose reabsorption, lowers blood glucose levels, and causes improved glucose control, faster metabolic effect, glucosuria, significant reduction in blood pressure, cardiovascular benefits, and reduced sympathetic overactivity, in type II diabetes mellitus patients [1-4].

Objective

The objective of this clinical pharmacological study is the prevailing prescription patterns appraisal of the combination therapies of metformin and remogliflozin, metformin and sitagliptin, and metformin and gemigliptin, among early grade type II diabetic patients.

Materials and Methods

Ethical Approval

At first, the Institutional Ethics Committee clearance and approval was taken for conducting this study. Then, this 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 global regulatory requirements. An informed consent was obtained from each patient.

Inclusion Criteria

The inclusion criteria for this study were as follows: (a) patients of any gender, (b) patients within 35 and 60 years, (c) patients presenting with early moderate grade, type II diabetes mellitus, (d) type II diabetes mellitus American Diabetes Association diagnostic criteria, (e) co-operative and conscious patients, (f) patients willing to undergo all pre and post-treatment investigations, (g) patients willing to complete the entire course of treatment, (h) patients who have given consent, (i) patients who are willing to go for a follow-up, (j) patients not taking any previous anti-diabetic drug, and (k) patients not taking any concomitant medication.

Exclusion Criteria

The exclusion criteria for this study were as follows: (a) uncooperative or unconscious patients, (b) patients below 35 and above 60 years, (c) patients presenting with any grade other than early moderate grade of diabetes, (d) patients with a history of hypersensitivity to any of the study drugs, (e) patients with high risk diseases or co-morbidities, (f) cardiac, renal or any other associated complications or co-morbidities, (g) any chronic disease intervening with the study data, (h) pregnant or lactating women, (i) paediatric or geriatric patients, (j) other associated medical illness or disorders, having impact on study results, and (k) female patients using hormonal contraceptives.

Study Type

This was a prospective, analytical study of the appraisal of the clinical prescriptions.

Study Population

The study population consisted of 90 treated type II diabetes mellitus patients, of early moderate grade, in tertiary diabetic healthcare centers.

Study Period

The study period, comprising of the periods for the research study and the compilation of the study literature, was 1 year and 9 months, from February, 2021 to August, 2021, and from January, 2022 to November, 2022.

Place of Study

This research study and the subsequent compilation of the study literature was done in the Departments of Pharmacology, Clinical Pharmacology, Molecular Pharmacology, Pharmacovigilance, Rational Pharmacotherapeutics, Evidence Based Medicine, Diabetology and Metabolic Medicine, Endocrinology, Clinical Medicine, Clinical Pathology, and Clinical Research, in Dr. Moumita Hazra's Polyclinic And Diagnostic Centre, Hazra Nursing Home, Hazra Polyclinic And Diagnostic Centre, Narayana Medical College, Narayana Hospitals, Rama Medical College Hospital and Research Centre, Rama University, Mamata Medical College and Mamata Hospitals.

Study Procedure

93 early moderate grade, type II diabetes mellitus patients, were prescribed oral 250 mg metformin and 50 mg remogliflozin combination therapy, or oral 250 mg metformin and 25 mg sitagliptin combination therapy, or 250 mg metformin and 25 mg gemigliptin combination therapy, once daily, for 3 months. The patients' demographic characteristics, diabetic symptoms assessment, and the patients' disease and disease-related history were recorded with a study proforma. Then, thorough general physical examination and systemic examination were performed on the patients under study. The relevant blood, urine and other investigations, like fasting and post-prandial blood sugar level, HbA1c level and urine routine examination findings, including sugar and albumin levels and microscopy, along with adverse drug reactions monitoring, were done at subsequent intervals, and follow-up, to confirm the progressing health status of the patients being treated. Patients' adherence criteria to the prescribed anti-diabetic drugs, like total study patients, total patients who completed the study, total lost to follow-up patients, total drop-out patients due to adverse effects, and total patients who had withdrawn voluntarily, were also analysed. The prevailing prescription patterns of the prescribed anti-diabetic combination therapies, were analysed. The number of prescriptions, prescribed for each combination therapy, was recorded; and the percentage of prescriptions for each drug, was calculated. Thorough prescription contents analysis, of all the 93 prescriptions, was done. The different aspects of the prescription contents, including the completeness of the prescription contents, completeness of the different aspects of the prescription format: (i) superscription: complete patient details, complete physician details, date, the sign 'Rx', (ii) inscription: number of prescribed drugs, drugs prescribed by generic names, appropriate drug of choice prescribed, economic drug prescribed, rational prescription, no irrational drug prescription, (iii) subscription: the dose of drug, the duration of treatment, the strength of the drug, the frequency of drug intake, the dosage form of the drug, the dosage route, (iv) transcription: language understandable by patient, complete instructions of medication, provisional or final diagnosis recording, doctor's signature, doctor's registration number, correct and properly written abbreviations, legible handwriting, capital letters, and permanent ink, were thoroughly analysed and recorded. The various derived observations were statistically interpreted as the prescription content analysis percentages.

Statistical analysis

The prescription contents evaluation was performed by different types of statistical

analyses in percentages, which were further illustrated graphically.

Results

The demographic characteristics of 93 early grade diabetic type II patients, receiving metformin and remogliflozin, metformin and sitagliptin, or metformin and gemigliptin combination therapies, were comparable. All study patients completed the study thoroughly, with no adverse effects related drop-out patients, lost to follow-up patients or voluntarily withdrawn patients. The patient adherence to the administered drug treatments was excellent. Among the prescribed combination therapies, metformin and sitagliptin was most commonly prescribed (67 prescriptions, 72.04%), followed by metformin and remogliflozin (19 prescriptions, 20.43%), which was followed by metformin and gemigliptin (7 prescriptions, 7.53%), as depicted in Graphical Illustration 1.

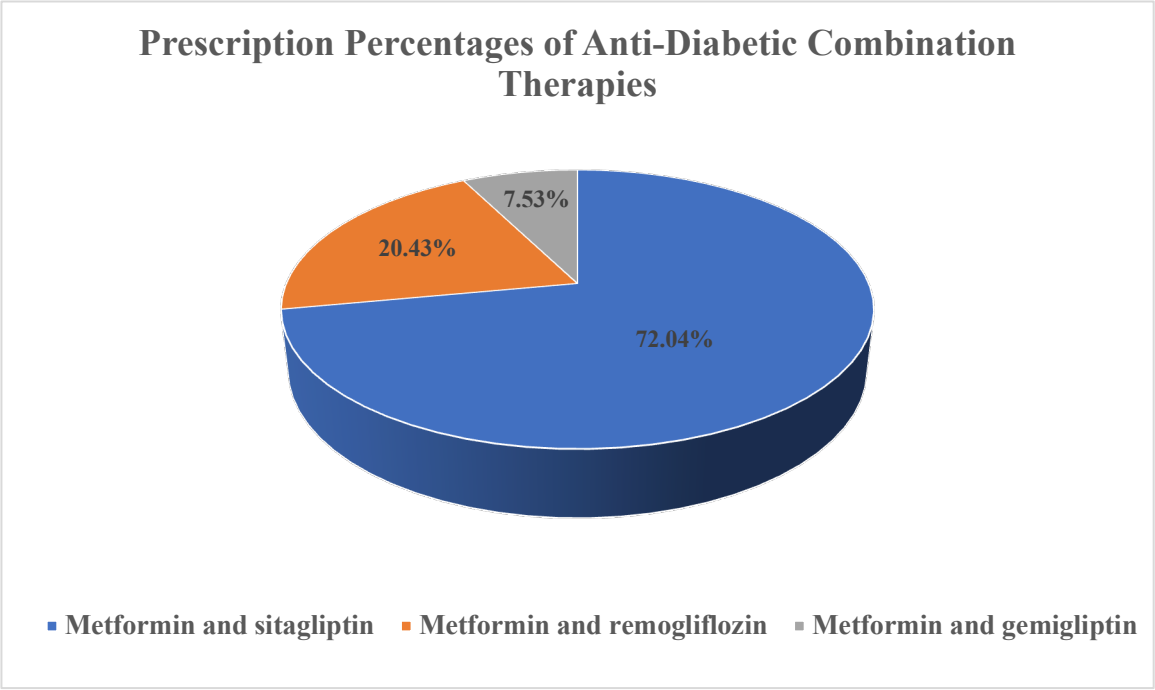

Figure 1: Prescription percentages of anti-diabetic combination therapies

The prescription rates of the anti-diabetic drugs combination therapies were as follows: metformin and sitagliptin > metformin and remogliflozin > metformin and gemigliptin.

The different aspects of the prescription contents, including the completeness of the prescription contents, completeness of the different aspects of the prescription format : (i) superscription : complete patient details, complete physician details, date, the sign 'Rx', (ii) inscription : number of prescribed drugs, drugs prescribed by generic names, appropriate drug of choice prescribed, economic drug prescribed, rational prescription, no irrational drug prescription, (iii) subscription : the dose of drug, the duration of treatment, the strength of the drug, the frequency of drug intake, the dosage form of the drug, the dosage route, (iv) transcription : language understandable by patient, complete instructions of medication, provisional or final diagnosis recording, doctor's signature, doctor's registration number, correct and properly written abbreviations, legible handwriting, capital letters, and permanent ink, were observed in all 93 prescriptions, that is, in 100% of prescriptions, as depicted in Table 1.

Table 1: Prescription content analysis for different anti-diabetic drugs combination therapies in 93 prescriptions.

Serial No.	Prescription Contents	Results n (%)
1.	Completeness of the prescription contents	93 (100%)
2.	Completeness of prescription format:	93 (100%)
i.	**Superscription:**	93 (100%)
a.	Complete patient details	93 (100%)
b.	Complete physician details	93 (100%)
c.	Date	93 (100%)
d.	Sign 'Rx'	93 (100%)
ii.	**Inscription:**	93 (100%)
a.	Number of prescribed drugs	93 (100%)
b.	Drugs prescribed by generic names	93 (100%)
c.	Appropriate drug of choice prescribed	93 (100%)
d.	Economic drug prescribed	93 (100%)
e.	Rational prescription	93 (100%)
f.	No irrational drug prescription	93 (100%)
iii.	**Subscription**	93 (100%)
a.	Dose of drug	93 (100%)
b.	Duration of treatment	93 (100%)
c.	Strength of drug	93 (100%)
d.	Frequency of drug intake	93 (100%)
e.	Dosage of drug	93 (100%)
f.	Dosage route	93 (100%)
iv	**Transcription**	93 (100%)
a.	Language understandable by patient	93 (100%)
b.	Complete instructions of medication	93 (100%)
3.	Provisional or final diagnosis recording	93 (100%)
4.	Doctor's signature	93 (100%)
5.	Doctor's registration number	93 (100%)
6.	Correct and properly written abbreviations	93 (100%)
7.	Legible handwriting	93 (100%)
8.	Capital letters	93 (100%)
9.	Permanent ink	93 (100%)

The prescribed combination therapies of metformin and sitagliptin, metformin and remogliflozin, and metformin and gemigliptin, had controlled early moderate grade type II diabetes mellitus, with significant decrease in the blood sugar levels and the HbA1c levels, in the successive 3 months. The adverse effects observed with the prescribed combination therapies, were statistically non-significant. Therefore, the combination therapies, were safe and tolerable.

Discussion

Diabetes mellitus is the most prevalent multi-system endocrinological disorder, spanning global pharmacoepidemiology. Therefore, this requires various regimen-wise combination therapies, which are more suitable for a comprehensive multi-system pharmacotherapeutic efficiency. In the recent times, there is an evident increase in the global clinical prescriptions of the combination therapies of metformin and remogliflozin, metformin and sitagliptin, and metformin and gemigliptin, among early grade type II diabetic patients, as these combinations have augmented and

well-manifested beneficial effects, although maintaining adequate safety and tolerability, as synergistic combination diabetological pharmacotherapeutics. These combination therapies also stabilise serum glycaemic levels and HbA1c levels, much faster. The absolute effectiveness of most oral hypoglycaemic medication rarely suffices the required ranges. Hence, initial combination therapy must be considered in patients presenting with HbA1c levels 1.5–2.0% above the target. Current treatment strategies for diabetes include biguanides, sulfonylureas, alpha-glucosidase inhibitors, thiazolidinediones, insulin and its analogs, dipeptidyl peptidase-4 inhibitors, and glucagon-like peptide analogs.

In this study, the demographic characteristics of 93 early grade diabetic type II patients, receiving metformin and remogliflozin, metformin and sitagliptin, or metformin and gemigliptin combination therapies, were comparable. The patient adherence to the prescribed drugs was very good, as because all the study patients completed the study thoroughly. There were no drop-out patients due to adverse effects, no patients who were lost to follow-up, and no patients who had voluntarily withdrawn. The most commonly prescribed regimen was the combination therapy of metformin and sitagliptin, which consisted of 67 prescriptions, comprising of 72.04% of the total prescriptions.

This was followed by the combination therapy of metformin and remogliflozin, which consisted of 19 prescriptions, comprising of 20.43% of the total prescriptions. This was finally followed by the combination therapy of metformin and gemigliptin, which consisted of 7 prescriptions, comprising of 7.53% of the total prescriptions. The prescription rates of the combination therapy of metformin and sitagliptin was more than the combination therapy of metformin and remogliflozin, which was in turn more than the combination therapy of metformin and gemigliptin.

Therefore, the prescription rates of the anti-diabetic drugs combination therapies, were as follows: metformin and sitagliptin > metformin and remogliflozin > metformin and gemigliptin. The prescription contents analysis had shown that in all the 93 prescriptions, there was 100% completeness of the prescription contents, and completeness of the different aspects of the prescription format : (i) superscription : complete patient details, complete physician details, date, the sign ‘Rx’, (ii) inscription : number of prescribed drugs, drugs prescribed by generic names, appropriate drug of choice prescribed, economic drug prescribed, rational prescription, no irrational drug prescription, (iii) subscription : the dose of drug, the duration of treatment, the strength of the drug, the frequency of drug intake, the dosage form of the drug, the dosage route, (iv) transcription : language understandable by patient, complete instructions of medication, provisional or final diagnosis recording, doctor’s signature, doctor’s registration number, correct and properly written abbreviations, legible handwriting, capital letters, and permanent ink.

Significant decrease in the blood sugar levels and the HbA1c levels was observed with the prescribed combination therapies of metformin and sitagliptin, metformin and remogliflozin, and metformin and gemigliptin, accompanied by adequate glycaemic stabilization among early moderate grade type II diabetic patients, within the successive 3 months. The adverse effects observed with the prescribed combination therapies, were statistically non-significant, thus validating these combination therapies to be safe and tolerable.

In different studies, along with the hypoglycaemic effect, the biguanide metformin has also demonstrated anti-neoplastic activities, involving both direct or insulin-independent, and indirect or insulin-dependent actions. Insulin has mitogenic and anti-apoptotic potentials. Thus, the anti-malignant pharmacodynamic

mechanisms, an indirect effect of metformin, with the reduced insulin levels, might be beneficially utilised, mostly for obesity and hyperinsulinaemia associated colon cancers, as well as breast cancers, associated with high levels of insulin receptor expression, cancer recurrence and death. As a direct pharmacological effect, metformin causes activation of AMP-activated protein kinase *via* phosphorylation on Thr172 by the tumor suppressor liver kinase B1, while consecutively reducing mammalian target of rapamycin mTOR signaling, protein synthesis and cell proliferation [5].

Several studies had revealed that sitagliptin, the anti-diabetic dipeptidyl peptidase inhibitor, also prevents diabetic complications, like diabetic nephropathy and vascular complications. The pharmacodynamic mechanisms of sitagliptin involved inhibition of HG-induced : (i) oxidative stress in HrGECs with decreased levels of mitochondrial reactive oxygen species (ROS), malondialdehyde (MDA), and 8-hydroxydeoxyguanosine (8-OHdG), (ii) production of pro-inflammatory cytokines interleukin-1β (IL-1β) and interleukin-8 (IL-8) in HrGECs, (iii) aggravation of HrGECs permeability, and (iv) reduction of the tight junction component claudin-5.

Sitagliptin also mediated the regulation of Kruppel Like Factor 6 (KLF6) and contained the HG induced pharmacological prophylactic effects of sitagliptin on endothelial monolayer permeability, thus decelerating the consequential oxidative stress, inflammation, and increased permeability in HrGECs. This emphasized on the potential role of sitagliptin in the prophylactic treatment of diabetic renal injuries [6].

Few studies had shown that sitagliptin had also manifested significant anti-inflammatory effects on the hypoxia-induced inflammation, and the oxidative stress which was induced by the enhanced production of reactive oxygen species (ROS) and decreased levels of reduced glutathione (GSH), in the endometrial stromal cells during endometriosis. Sitagliptin also significantly reduced the exaggerated production of the inflammatory mediators, like tumor necrosis factor (TNF)-α, interleukin (IL)-6, monocyte chemoattractant protein-1 (MCP-1), cyclooxygenase-2 (COX-2), prostaglandin E2 (PGE2), and high mobility group box (HMGB)-1, in hypoxia-treated HESCs; as well as, inhibited the hypoxia-induced activated p38 mitogen-associated protein kinases (MAPK) pathway in the HESCs. Sitagliptin even mitigated the hypoxia-induced phosphorylation and degradation of IκBα, the upregulation of nuclear factor kappa-B (NF-κB) p65 and the increased transcriptional activity of NF-κB [7].

In certain other studies, gemigliptin, another anti-diabetic dipeptidyl peptidase inhibitor, had comparatively superior effects on glycated haemoglobin (HbA1c), fasting plasma glucose, homeostatic model assessment beta cell function (HOMA-β), and LDL. Gemigliptin was also more effective in a HbA1c and HOMA-β Bayesian inference analysis, and was statistically significant in a HbA1c and HOMA-β sensitivity analysis [8].

In diabetes and hypertension co-morbidities, besides the type II anti-diabetic activity of sodium-glucose co-transporter 2 (SGLT-2) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), and dipeptidyl peptidase-4 (DPP-4) inhibitors, beneficial pleiotropic cardiovascular pharmacological effects, including anti-hypertensive action, were also demonstrated by these drugs, which were further acknowledged in the 2019 European Society of Cardiology or European Association for the Study of Diabetes guidelines on diabetes, prediabetes, and cardiovascular diseases.

Apart from the new insulin-dependent approach of SGLT2 inhibition in anti-diabetic treatment, greater anti-hypertensive effect was also achieved;

although DPP-4 inhibitors had shown the mildest anti-hypertensive effect [9].

Conclusion

Among the prescribed anti-diabetic combination therapies, metformin and sitagliptin was most commonly prescribed (67 prescriptions, 72.04%), followed by metformin and remogliflozin, which was followed by metformin and gemigliptin. The completeness of the different aspects of the prescription contents was 100%.

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