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ADDITION OF VOGLIBOSE TO THE DUAL COMBINATION THERAPY OF GLIMEPIRIDE AND METFORMIN IN THE MANAGEMENT OF TYPE 2 DIABETES

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KEYWORDS :

Type 2 diabetic patients are often treated with a combination of antidiabetic agents. The need to use drugs with different and complementary mechanisms of action frequently arises in daily clinical practice. There are several reasons to do this; namely, the disease itself is progressive, with the deterioration of glycemic control over time, and monotherapeutic attempts to achieve and maintain glycemic control often fail in the long run[1]. Some patients do not accept insulin treatment because of the fear of needles and injections, the fear that the complications of diabetes are caused by insulin, and other false beliefs, and are willing to take as many anti-diabetic pills. Several pharmacological agents have been developed to treat patients with type 2 diabetes mellitus. They either improve insulin resistance (biguanides and thiazolid ine diones), stimulate insulin secretion from the -cell (sulphonyl ureas and metaglinides), or decrease glucose absorption from the gut (α-glucosidase inhibitors)[2]. Metformin monot he rapy is initially recommended along with lifestyle modifica tions (increased physical activity and weight loss) for glycemic management of type 2 DM. However, if glucose levels are not controlled in patients with type 2 diabetes, other classes of antidiabetic agents are then additionally required. Coadministration of glimepiride and metformin has been used to achieve glucose control[3].

Combination therapy using sulfonylurea and metformin, which respectively promotes insulin secretion and improves insulin resistance, is an effective and complementary method that improves both of the main causes of type 2 diabetes and has been reported by UKPDS and other clinical studies to be more effective than monotherapy of both drugs[4]. Metformin improves insulin resistance and is recommended as the first-choice medication for newly diagnosed type 2 diabetes patients by most guidelines. Glimepiride is a third-generation sulfonylurea that stimulates insulin secretion. Unlike conventional sulfonylurea, glimepiride has high selectivity toward the pancreatic ATP-sensitive potassium channel, increases glucose transport, and shows various extrapancreatic effects in muscle and fat cells. For these benefits, glimepiride is prescribed as a primary monotherapy or additional medication when metformin monotherapy has failed. Various trials have established the efficacy of the combination of metformin with glimepiride. Kim et al. compared the efficacy and safety of early combination therapy with glimepiride/metformin to metformin up-titration in reducing glycated hemoglobin (HbA1c) levels in Korean type 2 diabetic patients inadequately controlled on low-dose metformin monotherapy. The study was a randomized, open-label, parallel-group, multicenter study, 209 Korean type 2 diabetic patients (HbA1c 7.0–10.0%, on metformin 500–1,000 mg/day) received glimepiride/metformin fixed-dose combination (G/M FDC) or metformin uptitration treatment (Met UP). The primary end-point was the change in HbA1c from baseline to week 24. G/M FDC therapy provided significantly greater adjusted mean decreases vs Met UP therapy in HbA1c (-1.2 vs -0.8%, $P < 0.0001$), and fasting plasma glucose (-35.7 vs -18.6 mg/dL, $P < 0.0001$). A significantly greater proportion of patients with G/M FDC therapy achieved HbA1c <7% (74.7 vs 46.6%, $P < 0.0001$) at the end of the study. A modest increase in mean body weight occurred in the patients who were treated with G/M FDC therapy (1.0 kg), whereas a slight decrease was observed in the patients who were treated with Met UP therapy (-0.7 kg). It was concluded that glimepiride/metformin fixed-dose combination therapy was more effective in glycemic control than metformin uptitration, and was well tolerated in type 2 diabetic patients inadequately controlled by low-dose metformin monotherapy in Korea[4].

Ortiz et al., compare the efficacy of glimepiride/metformin combination versus glibenclamide/metformin for reaching glycemic control in patients with uncontrolled type 2 diabetes mellitus. A randomized, double-blind, multicenter clinical trial was performed in 152 uncontrolled type 2 diabetic patients. Serum fasting and postprandial glucose, hemoglobin A1c (A1C), high-density lipoprotein cholesterol, and triglycerides were measured. Each study group included 76 patients. No significant differences in basal clinical and laboratory characteristics between groups were found. At the end of the study, A1C concentration was significantly lower in the glimepiride/metformin group (P=.025). A higher proportion of patients from the glimepiride group (44.6% vs. 26.8%, Pb.05) reached the goal of A1C b7% at 12 months of treatment. A higher proportion of hypoglycemic events were observed in the glibenclamide group (28.9% vs. 17.1%, Pb.047). It was found that Glimepiride/metformin demonstrated being more efficacious than glibenclamide/metformin at reaching the glycemic control goals with less hypoglycemic events in patients with uncontrolled type 2 diabetes mellitus[5]. Young Park et al., compare the commonly prescribed oral anti-diabetic drug (OAD) combinations to use as add-on therapy with insulin glargine in patients with uncontrolled type 2

diabetes despite submaximal doses of OADs. 99 patients with inadequately controlled type 2 diabetes were randomly assigned on a 1:1:1 basis to receive insulin glargine, with fixed doses of glimepiride, metformin, and glimepiride plus metformin. Outcomes assessed included HbA1c, the changes in fasting glucose levels, body weight, serum lipids values, insulin dose, and symptomatic hypoglycemia. After 24 weeks, HbA1C levels improved from (mean ± SD) 8.5±0.9% to 7.7±0.8% (69.0±10.0 mmol/mol to 60.8±8.6 mmol/mol) with insulin glargine plus metformin, from 8.4±1.0% to 7.7±1.3% (68.8±10.6 mmol/mol to 61.1±14.4 mmol/mol) with insulin glargine plus glimepiride and from 8.7±0.9% to 7.3±0.6% (71.7±9.8 mmol/mol to 56.2±6.7 mmol/mol) with insulin glargine plus glimepiride plus metformin. The decrease in HbA1c was more pronounced with insulin glargine plus glimepiride plus metformin than with insulin glargine plus metformin (0.49% [CI, 0.16% to 0.82%]; P = 0.005) (5.10 mmol/mol [CI, 1.64 to 8.61]; P = 0.005) and insulin glargine plus glimepiride (0.59% [CI, 0.13% to 1.05%]; P = 0.012) (5.87 mmol/mol [CI, 1.10 to 10.64]; P = 0.012) (overall P = 0.02). Weight gain and the risk of hypoglycemia of any type did not significantly differ among the treatment groups. It was concluded that the combination therapy of metformin and glimepiride plus glargine insulin resulted in a significant improvement in overall glycemic control as compared with the other combinations[6].

Although the combination of a sulfonylurea with metformin is commonly used in clinical practice, however, when this potent combination is no longer able to provide acceptable glycemic control, the addition of an antidiabetic drug with a different mode of action may lead to improved metabolic control[1]. The addition of the second agent usually lowers the mean HbA1c level of 1.0 to 1.4% more than monotherapy when the baseline value is between 8.5% and 9.5%. Thus by using dual therapy and when the HbA1C is >9 it is not possible to achieve the desired HbA1C target i.e. <6.5%. Thus, it is proposed that a third agent with a different mechanism of action can be added to the existing dual therapy if the HbA1c level achieved with two agents is 8.0% or less. It has been observed that postprandial glucose level plays a major role in complications, thus besides controlling the fasting glucose, it is very important to control the postprandial glucose level aggressively. Thus a triple-drug combination is suggested that can specifically control postprandial hyperglycemia by reducing intestinal glucose absorption[7]. A combination of voglibose, metformin and glimepiride is one such combination. All three drugs act by different mechanisms and can control both fasting and postprandial glucose levels.

Voglibose is an alpha-glucosidase inhibitor, known for its ability to increase and prolong glucagon-like peptide-1 (GLP-1) secretion in T2DM subjects which shows inhibitory action on glucagon secretion and lowers fasting glucose levels. Increased release of GLP-1, which is an insulinotropic hormone, enhances insulin secretion and insulin sensitivity. It also delays the absorption as well as digestion of dietary polysaccharides by reversibly inhibiting carbohydrate digestive enzymes. Voglibose has shown to improve glucose tolerance by inhibiting digestion, absorption of glucose from the intestine and decrease postprandial glucose without inducing over secretion of insulin[8].

Trials have established the efficacy of the combination of voglibose and metformin. Oh et al., compared the efficacy and safety of a fixed-dose combination of voglibose plus metformin (vogmet) with metformin monotherapy in drug-naïve newly-diagnosed type 2 diabetes mellitus. A total of 187 eligible patients aged 20 to 70 years, with a glycosylated hemoglobin (HbA1c) level of 7.0% to 11.0%, were randomized into either vogmet or metformin treatments for 24 weeks. A change in the HbA1c level from baseline was measured at week 24. The reduction in the levels of HbA1c was −1.62%±0.07% in the vogmet group and −1.31%±0.07% in the metformin group (P=0.003), and significantly more vogmet-treated patients achieved the target HbA1c levels of <6.5% (P=0.002) or <7% (P=0.039). Glycemic variability was also significantly improved with vogmet treatment, as estimated by M-values (P=0.004). Gastrointestinal adverse events and hypoglycemia (%) were numerically lower in the vogmet-treated group. Moreover, a significant weight loss was observed with vogmet treatment compared with metformin (−1.63 kg vs. −0.86 kg, P=0.039). It was concluded that Vogmet is a safe antihyperglycemic agent that controls blood glucose level effectively, yields weight loss, and is superior to metformin in terms of various key glycemic parameters without increasing the risk of hypoglycemia[9]. Faruqui., carried out post-marketing surveillance (PMS), non-randomized, open, non-comparative, mono-centric study. The drug administered was a fixed-dose combination of voglibose 0.2 mg; glimepiride, 0.5 mg, and metformin 500 mg sustained-release (SR). Fifty type 2 diabetic patients were given a fixed-dose combination twice daily with major meals for 3 months. Baseline value was recorded for glycated hemoglobin (HbA1c), fasting plasma glucose (FPG) and postprandial blood glucose/hyperglycemia (PPHG) level. It was found that there was a significant decrease from baseline in HBA1c value 10.6 ± 1.3 vs. 6.6 ± 0.4 (P< 0.0001), FPG levels 208.33mg/dl vs. 118.06 (P< 0.0001), and PPHG levels 360.14 mg/dl vs. 168.36, (P< 0.0001) after 3 months of treatment. The combination was found to be effective in controlling both fasting and postprandial glucose levels and was well tolerated. Investigator commented that the use of triple-drug combination is a good option in the management of type 2 diabetes which controls both fasting as well as postprandial blood glucose and ultimately HbA1c values[10].

CONCLUSION

Metformin has been the mainstay and first-line treatment for the management of type 2 diabetes. However, the management of type 2 diabetes often requires a combination of antidiabetic agents. For the successful management of both insulin resistance and cell dysfunction, there arises a need for combination therapy with agents having complementary mechanisms of action. The outcome of clinical trials like UKPDS laid the basis of usage of metformin along with glimepiride. To further maintain glycemic control, a triple combination of voglibose and metformin & glimepiride has been proposed. Trials have confirmed the efficacy and safety of this triple combination, though large scale trials are needed. Used wisely, with adequate medication counseling, triple FDCs provide effective glycemic control in a safe, well-tolerated, and economic manner.

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