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THE COMPREHENSIVE GLYCAEMIC CONTROL USING THE TRIPLE COMBINATION- VOGLIBOSE, GLIMEPIRIDE, METFORMIN

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INTRODUCTION

Diabetes mellitus is one of the most prevalent metabolic diseases in the world. Type 1 diabetes is due to insulin deficiency affecting about 5-10% of the diabetic population, whereas type 2 is most common which occurs mainly due to insulin resistance. Diabetes is one of the leading causes of morbidity and mortality characterized by hyperglycemia that is associated with several complications including neuropathy, nephropathy, heart disease, stroke and vascular diseases [1]. Current therapeutic approaches to treat type 2 diabetes include oral antidiabetic drugs such as sulfonylureas, thiazolidinediones, metformin, a-glucosidase inhibitors, and glycosuric. New therapies include peptides such as glucagon-like peptide-1 (GLP-1) agonists (exenatide, liraglutide), and dipeptidyl peptidase-IV (DPP-IV) inhibitors (sitagliptin, vildagliptin). Emerging therapies include cannabinoid receptor type 1 antagonists and bile acid sequestrants[1]. Lifestyle modifications and monotherapy with oral hypoglycemic agents are generally considered as a first-line intervention for glycemic control in type 2 diabetes. However, as the disease progresses, β cells continue to deteriorate in type 2 diabetes patients who require effective glycemic control. Most often, the efficacy of monotherapy decreases after few years of treatment resulting in ineffective glycemic control and does not prevent the progression of the disease, which requires the addition of a new drug in the therapeutic regime for effective glycemic control. For the successful management of both insulin resistance and β cell dysfunction, there arises a need for combination therapy with agents that have complementary mechanisms of action

formulated as a single dosage form called "Fixed-Dose Combinations" (FDCs)[2].

Advantages of FDCs[2]

- FDCs help in formulating two drugs into a single dosage form, thereby minimizing the medication burden to the patient.
- The relative therapeutic adherence rates of type 2 diabetes patients can be improved.
- It improves glycemic control showing better efficacy.
- Medical expenditures due to hospitalization can be reduced.
- It decreases the frequency of drug administration in patients with type 2 diabetes.
- It prevents polypharmacy

Type 2 diabetes mellitus is a complex and progressive disease. Earlier, type 2 diabetes mellitus was thought to be only a disease of insulin resistance, however current findings indicate the involvement of at least eight pathologic processes that lead to type 2 diabetes mellitus[3]. Thus, combining the drugs that have different mechanisms of action, an FDC of two or three-drug to provide an intensive initial blood glucose management seems to be a logical regimen. This will help to simultaneously regulate the fasting as well as the postprandial blood glucose in diabetic patients, and thereby delaying the progression of the disease[4].

Metformin has been used for over 40 years as a first-line oral hypoglycemic agent in type 2 diabetes that suppresses hepatic glucose production, restores insulin secretion, and improves insulin sensitivity. It is generally chosen as the first drug in the treatment of type 2 diabetes because of its proven efficacy in lowering blood glucose and sustaining weight loss, low risk of hypoglycemia, and cost-effectiveness. In the case of metformin monotherapy failure, the addition of another hypoglycemic agent that acts according to a mutually complementary mechanism is recommended to ensure adequate glycemic control[5].

The United Kingdom Prospective Diabetes Study (UKPDS 49) compared the different treatment regimes, with diet alone, insulin, a sulfonylurea, or metformin (mean follow-up, 9 years) in 4075 patients with newly diagnosed type 2 diabetes. In the subgroup that received monotherapy, a sulfonylurea (normal-weight and overweight patients) or metformin (overweight patients), target HbA1c concentrations were not maintained in 50% and 76% of patients who received monotherapy with a sulfonylurea and in 56% and 87% of patients who received monotherapy with metformin at 3 and 9 years of treatment, respectively[6]. Further, the UKPDS reported that the proportion of patients in whom an HbA1c concentration <7% was achieved increased from 21% to 33% with the addition of metformin to a regimen of monotherapy with a sulfonylurea ($P < 0.05$)[6]. This apparent additive efficacy might be explained by the complementary mechanisms of antihyperglycemic action of the 2 drugs (ie, the stimulated insulin secretion of pancreatic β cell by the sulfonylurea and the enhanced insulin sensitivity of the hepatic and peripheral tissues by metformin)[7]. The sulfonylurea, glimepiride, seems to offer some advantages as a component for an FDC with metformin due to its more prominent extrapancreatic activity and a more favorable safety profile compared with those of other sulfonylureas[8,9]. Glimperaide binds to the sulfonylurea receptor on the membrane of the pancreatic β cells to stimulate endogenous insulin production, a mechanism that is distinct from and thus complementary to the blood-glucose-lowering effects of metformin.

In a randomized, forced-titration study by Umpierrez et al, which enrolled 203 patients whose type 2 diabetes was inadequately controlled (HbA1c, 7.5%–10.0%) with metformin monotherapy administered for ≥8 weeks[10]. The addition of glimepiride (initial dose, 2 mg/d, titrated to 8 mg/d for 6 weeks) to the metformin regimen for a total of 28 weeks was associated with a significantly shorter time

to achieve target HbA1c concentration (≤7%) (median, 80–90 days vs 140–150 days; P < 0.05), lower total cholesterol (–3.5 vs 12.2 mg/dL, respectively; P < 0.05), and lower LDL-C (–0.1 vs 8.5 mg/dL; P < 0.05) compared with pioglitazone add-on therapy (initial dose, 30 mg/d, titrated to 45 mg/d for 12 weeks)[10].

A combination of metformin with glimepiride is one of the widely utilized combinations for maintaining blood glucose levels in type 2 diabetic patients. The sulfonylurea drugs have similar blood glucose-lowering effects to metformin and reduce HbA1c from an average baseline of around 8.0% (64 mmol/mol) by a mean or median of 0.8%-1.0% (9-11 mmol/mol) when added to metformin in dual combination therapy[11,12]. However, their glycemic efficacy depends on the time after initiation in monotherapy studies, with a relatively potent effect in the first 3 to 6 months which wanes progressively over the next 1 to 2 years. Given that type 2 diabetes is characterized by the continuing loss of β-cell function, this time-dependent therapeutic failure may be more pronounced when sulfonylureas are combined with metformin since insulin secretory capacity is likely to be less in a patient who has progressed to two blood glucose-lowering therapies rather than one[13]. This poses an extremely difficult problem for maintaining blood glucose levels over a longer duration.

Thus, to have comprehensive and prolonged control over prandial as well as postprandial glucose levels, the addition of third component viz., an α-glucosidase inhibitor, is a promising approach. Voglibose, an α-glucosidase inhibitor, is widely used in the management of type 2 diabetes. It undergoes minimal systemic absorption. Voglibose delays the absorption of carbohydrates due to competitive inhibition of α-glycosidase in the small intestine. Consequently, voglibose inhibits the postprandial increase in plasma glucose levels, leading to decreased diurnal insulin secretion[4]. An FDC of voglibose, glimepiride, and metformin is intended to provide an intensive initial blood glucose management regimen in newly diagnosed diabetic patients by simultaneously regulating the fasting as well as the postprandial blood glucose, and thereby delaying the progression of the disease[4].

Murthy et al, compared the change in BMI, fasting and postprandial blood glucose, glycosylated hemoglobin (HbA1c), Glomerular Filtration Rate (GFR), serum creatinine, blood urea and lipid profile levels when two different therapies (group A = metformin+glimepiride) and group B = metformin+glimepiride+voglibose) are given to diabetic patients to compare efficacy of voglibose as an add-on therapy[14]. This study was a 10 months prospective, open-label comparative study. Type II diabetic subjects, aged >18 years were selected and were divided into groups A and B and dosed accordingly. It was found that groups A and B exhibit a significant decrease in BMI with p<0.017 and p<0.049, respectively. Although, in both groups' glucose triad levels decreased significantly. There was no effect found over the blood urea level. However, improvement in protective function of kidney was observed when voglibose was added to the therapeutic regime in group B. Evidence of significantly improved lipid profile was also observed in triple-drug therapy, group B. It was concluded that the addition of voglibose to dual therapy comprising of glimepiride and metformin, showed a very significant benefit in controlling the glucose triad levels (HbA1C, fasting plasma glucose and postprandial glucose level) as well as nephroprotective effect when compared to dual therapy. Further, voglibose was also found to decrease Total Cholesterol (TC), triglycerides (TGs) and Low-Density Lipoproteins (LDL) level and increase HDL significantly[14].

Theoretically, this FDC of voglibose, glimepiride, and metformin also has the potential to neutralize the potential side-effects as well. The possibility of weight gain with

sulphonylureas may be neutralized by the weight loss properties of metformin and voglibose. Since metformin and voglibose increase glucagon-like peptide-1 levels, additive action may be present while using their combination[15].

CONCLUSION

An FDC of voglibose, glimepiride and metformin seem to be a promising and rational therapeutic regime for comprehensive and prolonged control over blood glycemic levels. The three drugs exert their therapeutic effect via different mechanism thereby reducing the possibility of early drug resistance. The potential of this triple drug FDC has also been demonstrated in a few clinical studies. However, further, larger and comprehensive clinical trials are required.

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