The combinatorial effective approach of alpha-glucosidase inhibitor and Sodium-glucose co-transporter 2 (SGLT-2)

Alok Raghav[1]*, *Jamal Ahmad*[2]

[1,2]Rajiv Gandhi Centre for Diabetes & Endocrinology, J.N. Medical College, Aligarh Muslim University, Aligarh

***Corresponding Author:** Alok Raghav, Rajiv Gandhi Centre for Diabetes & Endocrinology, J.N. Medical College, Aligarh Muslim University, Aligarh E-mail: alokalig@gmail.com

ABSTRACT

Sodium glucose co-transporter type 2 (SGLT2) inhibitors are novel class drugs implicate in the treatment of type 2 diabetes mellitus (T2DM). These classes target the kidney and reduce the glucose reabsorption thereby promoting glucose excretion resulting in hyperglycemia reduction. Alpha-glucosidase inhibitors (AGIs) are the combinatorial choice mainly acts by inhibiting the absorption of carbohydrates from the gut. Metformin remains the preferred drug for monotherapy, but according to new statistical clinical results, SGLT2 inhibitors coupled with AGIs would serve as the choice for second and third line therapy in management T2DM.

INTRODUCTION

Sodium-glucose co-transporter 2 (SGLT2) inhibitors present novel approach of anti-hyperglycemic classes of drugs of the 21st century. SGLT2 showed dramatically reductions in the episodes of cardiovascular (CV) mortality, blood pressure, and body weight in patients with T2DM (1-2). Since SGLT2 results in effective weight loss may be the first choice of medication in the management of T2DM subjects presenting obesity. Furthermore, with new framed recommendations of American Diabetes Association (ADA)/ European Association for the Study of Diabetes (EASD) suggested the addition of SGLT2 inhibitors in combination with metformin or sulfonylureas in glycemic goals are not achieved.

In another study, Leiter et al. (3) evaluate the efficacy and safety of canagliflozin (dose 100 or 300 mg/day) compared to glimepiride in T2DM subjects. Surprisingly the metabolic effect of SGLT2 does not depend on the insulin-dependent mechanism. These inhibition approaches with SGLT2 prove to be effective when used with other agents causing reduction of hyperglycemia in T2DM subjects. In a randomized double-blind placebo-controlled trial by Neal et al. (4) concluded that there is a significant reduction in plasma glucose, body weight, and hypertension when SGLT2 (i.e canagliflozin) added with insulin therapy.

SGLT2 inhibition action possesses the blockade of SGLT1, the transporter for glucose uptake from intestinal lumen causing reduction of postprandial glucose (5). SGLT2 causes weight loss by sodium

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ions clearance that furthermore contributes to the reduction of edema and hypertension.

In the combinatorial choice of second-line therapy, Alpha-glucosidase inhibitors (AGIs) are a popular choice for management of T2DM. These inhibitors cause delayed carbohydrate absorption from the walls of the small intestine, thereby causing a reduction in postprandial glucose. The recommendation guidelines to use AGIs for controlling glycemic targets appears to be different, for instance, European Diabetes Policy Group and American Diabetes Association statement is not specific. A recent review on the use of acarbose (AGIs) has a decreasing effect on HDL and LDL in T2DM subjects (6). In another meta-analysis study with seven trials demonstrate the reduction of myocardial infractions in T2DM with acarbose (7).

A Cochrane systemic meta-analysis review investigated the role of AGIs versus placebo with respect to mortality, morbidity, strict glycemic control, lipids, body weight and side effects. The results concluded that 41 studies (30 acarbose, 7 miglitol, 1 voglibose, 3 combinations) there was no evidence of morbidity and mortality (8).

Mechanism of action of SGLT2 inhibitors

SGLT2 mediate the active transport of glucose into urine via the kidney. In a healthy person, kidney filters approx 180 g glucose per day which was re-absorbed and returned into the bloodstream. In diabetes mellitus increased plasma glucose concentration results n excess glucose in the bloodstream that can be beyond the threshold of re-absorption, thereby excreted into the urine. The SGLT2 inhibition potentially reduces renal glucose reabsorption and enhances excretion of glucose into the urine (glucosuria) thereby causing a progressive decrease in hyperglycemia (9). Another study coated that familial renal glucosuria (genetic defect of SGLT2 gene) cause's excretion of less than 10 g/day of more than 200 g/day glucose into the urine (10).

Mechanism of action of alpha-glucosidase inhibitors

Dietary carbohydrate presents as oligo-or-polysaccharides that have to be simplified into monosaccharides for digestion. Starch is digested via two-step mechanisms, by alpha-amylase chopping into disaccharides prior sucrose, isomaltase, maltase, and lactase cuts it to digestible monosaccharides (11).

Acarbose (AGIs) inhibits alpha-amylase along with other alpha-glucosidase thus preventing digestion and absorption of dietary starch into simpler monosaccharides (12). Voglibose and miglitol (AGIs) show inhibition of disaccharide digesting enzymes, but no effect on alpha amylase. This AGIs class delays absorption of intestinal carbohydrate, thereby controlling post prandial plasma glucose and help in the management of T2DM.

Conclusion

SGLT2 inhibitors are first-line of treatment for T2DM but can be effectively implemented with the use of AGIs as a combinatorial approach. AGIs alone can't control glycemic target due to flatulence and other gastrointestinal (GI) side effects and lower efficacy. So SGLT2 may be used as primary approach with background approach of AGIs for effective management of T2DM.

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