ERTUGLIFLOZIN-RISKS AND BENEFITS IN TYPE-2 DIABETES MELLITUS PATIENTS

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ABSTRACT: The risks and benefits of Ertugliflozin in Type-2 Diabetes mellitus patients. Ertugliflozin is sodium glucose co-transporter-2 (SGLT2) inhibitors and is considered as 3rd line agent for Diabetes mellitus therapy. It is a novel kind of Anti-hyperglycemic agent approved by the US FDA. The risk of Ertugliflozin is seen in genital infections and also in cardio vascular diseases. The benefits include no weight gain and a significant reduction in HbA1c, fasting plasma glucose, blood pressure levels and diastolic blood pressure when given in combination with metformin and sulfonylureas. Where Metformin and sulfonylureas which are commonly used as combination for treatment of Type-2 Diabetes mellitus.

KEY WORDS: Ertugliflozin, combination treatment with metformin and sulfonylurea's (sus), Risks (Genital Mycotic infection) and Benefits (No weight gain), reduction in HbA1c, Fasting plasma glucose, blood pressure, diastolic blood pressure.

INTRODUCTION:

Diabetes Mellitus (DM) is a chronic disorder characterized by hyperglycemia due to result of defect in insulin secretion(or) insulin action (or) both. The hyperglycemia is due to the increased concentration of glucose which is to be converted into energy in the presence of insulin hormone. 1. Polyuria (increased renal threshold, increased excretion of urine+glucose), 2. Polyphasia –excessive hunger, weight loss(due to breakdown of protein and fats in order to provide energy in absence of glucose metabolites),3.Polydypsia – excessive thrist due to increased renal threshold, 4.Glucosuria-excess glucose in urine,5. Ketoacidosia-excess ketone in urine ,6.Blurred vision ,7. Fatigue are the most common symptoms associated with Diabetes Mellitus. Furthermore Diagnostic Test include –1.Physical Examination (3 poly) symptoms, 2.Blood Test , 3.Glucose Tolerance Test , 4. HBA1C /Glycated haemoglobin. The treatment option include the use of Antihyperglycemic drugs. Those are 1.Biguanides(Metformin), 2.Sulfonyl ureas (glipizide ,glimepiride ,canagliflozin , ertugliflozin),3.Meglitinide(repaglinide and nateglinide),4.Thiazolidinediones (rosiglitazone,pioglitazone),5.Alpha-Glycosidase inhibitors (acarbose,miglitol,voglibose).Now-a-days, Ertugliflozin is used in combination with metformin and sulfonylureas to treat type 2 diabetes mellitus.**(1)**

Ertugliflozin is an oral, specific SGLT2 inhibitors **(2)**. Ertugliflozin is the 4th SGLT2 inhibitors which is approved by the US FDA in December 2017, for patients who are suffering with Type-2 Diabetes Mellitus **(3)**. SGLT2 inhibitors decrease renal tubular glucose reabsorption from the Proximal convoluted Tubule of the Kidney **(4)**, by which enhancing urinary glucose excretion and reducing plasma glucose and HbA1c (5), without leading to excessive insulin secretion in patients with Type-2 Diabetes Mellitus (6). SGLT2 inhibitors are free from beta cell function and insulin responsiveness is not related with hypoglycaemia when used monotherapy and associated with weight reduction **(7-10)** and has cardiovascular and renal benefits **(11-17)** due to which recent guidelines statements are recommending the use of SGLT2 inhibitors prior in therapy algorithm for patients with Type-2 Diabetes Mellitus with an expanded risk of cardiovascular disease and those with chronic kidney disease **(18-19)**. Expanded risk of Genital Mycotic infections, urinary tract infections (UTI), Symptomatic hypoglycemia and hypovolaemia **(3)** and Atherosclerotic cardiovascular disease **(2)**. Furthermore, benefits include weight reduction, a decrease in HbA1c, Fasting plasma glucose (FPG) levels, blood pressure and Diastolic blood pressure **(2,3,4,20, 43)**.

DISCUSSION:

In Diabetes Mellitus, the worldwide estimates indicate that its prevalence is expanding every year, with around 90% of Type-2 Diabetes Mellitus cases **(20)** .Cardiovascular Diseases are the leading cause of illness and death in patients with Type-2 Diabetes Mellitus **(21,22,23)** .Diabetes is a typical constant, Chronic disease Worldwide and is associated with the adverse socio-economic outcomes **(24)** .Type-2 Diabetes Mellitus is a progressive disease that gets worsen with disease progression **(25,26)** . Type-2 Diabetes Mellitus is likewise a significant risk factor for the development of heart failure and progression of renal disease **(27,28)**.

Metformin and SUS stay a usually used combination therapy because of their glycemic viability, minimal expense and conventional mechanisms of actions **(25,26)**. The metformin decreases digestive ingestion of glucose, there by decreases hepatic glucose production and further improve insulin sensitivity **(29,30)**. Where as SUS are effective in reducing glycated haemoglobin (HbA1c) **(31)**. Metformin (1st line therapy) **(32)** when used in combination with SUS (2nd line therapy) (33) they are causing weight gain and a higher occurrence of hypoglycemia than other Antihyperglycemic agents (AHAS) **(34,35)**. Although numerous Antihyperglycemic agents have already been available for treatment of Type-2 Diabetes Mellitus, their glucose-bringing down impact with regards to longterm glycemic control is not satisfactory **(36)**. There is an urgent need for more effective agents with less adverse effects to lower blood glucose **(36)**. When additional glycemic control is required and the choice is made to add 3rd oral AHA to the current metformin + SUS regimen sodium glucose co-transporter 2 (SGLT2) inhibitors might be attractive choice **(5)**.

SGLT2 inhibitors approved in the united states **(37)**. By decreasing the renal tubular glucose reabsorption from proximal convoluted tubule of kidney ,there by improving urinary glucose excretion and reducing plasma glucose and HbA1c **(5)** .SGLT2 inhibitors are free of beta cell function and insulin responsiveness,are not associated with hypoglycaemia when used as monotherapy, and are associated with weight loss **(7-10)** and have cardiovascular and renal benefits**(11-17)** By decreasing the renal glucose threshold and therefore increasing urinary glucose excretion ,the pharmacological inhibition of SGLT2 co-transporters decreases hyperglycemia ,offering an effective way to treat T2DM patients **(44)** .

SGLT2 inhibitors are novel kind of Anti hyperglycemic agents ,approved by US Food and Drug Administration (FDA) in 2013 including Canagliflozin ,Dapagliflozin ,Empagliflozin and Ertugliflozin **(37)** .Ertugliflozin is 4th SGLT2 inhibitors approved by US FDA in December 2017 ,for patients with T2DM(38) .Ertugliflozin is an oral ,specific SGLT2 inhibitors **(2)** whose absorption is rapid and complete , with tmax (peak plasma time) occurring 1-2 hours post –dose and almost 100% oral Bioavailability .The half life (t ½)is ranged from 11-18 hours , implying once daily administration **(3)** .

Ertugliflozin as monotherapy **(39)** or in combination with other Anti hyperglycemic agents has been associated with improvements in glycemic control, body weight and blood pressure **(40)**. However, in 2018, the FDA issued a Warning that SGLT2 inhibitors detailed instances of extreme genital infections **(37)**. Despite the fact that Ertugliflozin makes a great hypoglycemic difference, Genital infections are an Adverse effect which deserves consideration **(41,42)**.

CONCLUSION: Ertugliflozin is not very effective when given as monotherapy, but it is very effective when given in combination with Metformin and Sulfonylureas and results in a significantly greater reduction in HBA1C, Fasting Plasma Glucose (glycemic control) and Body Weight. Reduction in Pulse pressure, Mean Arterial Pressure, Systolic blood pressure and Diastolic blood pressure without an increase in pulse rate. While prescribing these drugs to Females a high consideration should be taken because these drugs are associated with genital infections. These drugs should be avoided (or) prescribed cautiously in case of patients who are already suffering from some cardiovascular disease (or) problem because these drug is associated with Atherosclerotic cardiovascular disease.

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