<u>**Educational Forum**</u>

Empagliflozin and Metformin

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USFDA has approved a new combination of Empagliflozin and Metformin in August 2015 for management of type-2 DM as an adjunct to diet and exercise to improve glycemic control in adults who are not adequately controlled on a regimen containing empagliflozin or metformin or in patients already being treated with both empagliflozin and metformin. Earlier European Medicines agency had given its approval to this combination in May 2015. This combination is not suitable for treatment of Type 1 DM or Diabetic Ketoacidosis.

Metformin is a Biguanide class of oral hypoglycaemic drug which increases the activity of AMP dependant protein kinase (AMPK). Activated AMPK stimulates fatty acid oxidation, glucose uptake, non oxidative metabolism and it reduces lipogenesis and gluconeogenesis. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day long plasma insulin response may actually decrease. [1] Empagliflozin is an orally active SGLT-2 inhibitor which reduces hyperglycemia by increasing urinary clearance of glucose. [1] When given in combination, it acts through different pathways to control glucose levels in type 2 DM patients. Drug combination is to be given twice daily with meals, with gradual dose escalation to reduce gastrointestinal side effects due to metformin. It is available in the form of tablets with Empagliflozin/Metformin in various dose combinations of 5mg/500mg, 5mg/1000mg, 12.5mg/500mg and 12.5mg/1000mg. Doses are to be adjusted based on effectiveness and tolerability while not exceeding maximum recommended dose of metformin 2000mg and empagliflozin 25mg. Bioequivalence studies have shown that all combination tablets are bioequivalent to coadministration of corresponding doses of empagliflozin and metformin as individual tablets. Administration of 12.5 mg empagliflozin/1000 mg metformin under fed conditions resulted in 9% decrease in AUC and a 28% decrease in Cmax for empagliflozin, when compared to fasting conditions. For metformin, AUC decreased by 12% and Cmax decreased by 26% compared to fasting conditions. The observed effect of food on empagliflozin and metformin is not considered to be clinically relevant. [2]

Most common adverse reactions associated with empagliflozin in various clinical trials were urinary tract infections and female genital mycotic infections, while metformin was associated with diarrhea, nausea/vomiting, flatulence, abdominal discomfort, indigestion, asthenia and headache. Use of this drug combination is contraindicated in patients of renal impairment, End stage renal disease or on dialysis and is not recommended for initiation/continuation in patients with serum creatinine levels greater than or equal to 1.5mg/dl for males and 1.4 mg/dl for females. Other contraindications include metabolic acidosis including diabetic ketoacidosis and history of serious hypersensitivity reaction to empagliflozin or metformin. There are no adequate and well controlled studies in pregnant women with this

combination or its individual components. Thus it should be used only if the potential benefit justifies the potential risks to the fetus. No studies in lactating animals have been conducted with combined components. In studies performed with the individual components, both empagliflozin and metformin were secreted in the milk of lactating rats. Safety and effectiveness of this drug in pediatric patients under 18 years of age have not been established.

Clinical studies

Empagliflozin Add-on Combination therapy with metformin- it was a double blind, placebo controlled study undertaken in total 637 patients with type 2DM to evaluate efficacy and safety of empagliflozin in combinatiom with metformin. Patients with type 2 diabetes inadequately controlled on at least 1500 mg of metformin per day entered an open label 2 week placebo run in. At the end of run-in period, patients who remained inadequately controlled and had HbA1c between 7 and 10% were randomozed to placebo, empagliflozin 10mg or 25 mg. At week 24, treatment with empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in HbA1c (p<0.0001), fasting plasma glucose and body weight compared with placebo. [3] In another study, a total 666 patients with type 2 diabetes participated in double blind, placebo controlled study to evaluate the efficacy and safety of empagliflozin in combination with metformin plus a sulfonylurea. Treatment with empagliflozin 10mg or 25mg daily provided statistically significant reductions in HbA1c (p<0.0001), fasting plasma glucose and body weight compared with placebo. [4] The combination helps to maintain euglycaemic levels in patients of type 2 diabetes mellitus who are not adequately controlled on metformin alone. But caution has to be taken in patients of impaired renal functions.

References

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