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SGLT-2 INHIBITORS AND INCRETIN BASED THERAPIES IN THE TREATMENT OF TYPE 2 DIABETES MELLITUS

General Medicine

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ABSTRACT

Incretin based therapies include the dipeptidyl peptidase 4 inhibitors (DPP4i) and the glucagon-like peptide 1 receptor agonists (GLP-1 RA). Oral DPP4i are approved for use in India. DPP4i can be used as monotherapy or in combination with other oral agents or with basal insulin. They are weight neutral and have a low risk of hypoglycaemia. GLP-1 RA are either analogs of human GLP-1 (liraglutide, dulaglutide, albiglutide) or are based on the exendin molecule (exenatide, lexisenatide). Clinical trials have shown that the GLP-1 RA effectively lower the blood glucose levels when used as a monotherapy or in combination with other drugs. Under physiologic conditions, SGLT-2 transporter in the renal proximal tubule reabsorbs 80-90% of the filtered glucose. SGLT-2 is primarily expressed in the kidney, but is also found in the α-cells. The latest National Institute for Health and Care Excellence (NICE) Guidelines recommend the use of metformin as the initial choice of therapy and a target HbA1c of <6.5% most patients.

KEYWORDS

Incretin based therapies include the dipeptidyl peptidase 4 inhibitors (DPP4i) and the glucagon-like peptide 1 receptor agonists (GLP-1 RA). The development of the incretin based treatment for type 2 diabetes mellitus (DM) are derived from the observation that the effects of oral glucose of stimulating insulin secretion is much greater than when glucose glucose levels are raised to the same concentration using intravenous glucose. The incretin hormones are secreted by the K-cells located in the duodenum and jejunum and the L-cells located in the distal small bowel and large intestine. The loss of incretin response may be the primary pathophysiological abnormality in the development of type 2 DM.[1]

DPP4i:-

Oral DPP4i are approved for use in India. DPP4i can be used as monotherapy or in combination with other oral agents or with basal insulin. They are weight neutral and have a low risk of hypoglycaemia. Meta-analysis of DPP4i showed an average HbA1c reduction of 0.74% which is slightly less efficacious than the sulfonylureas when used as monotherapy and similar to metformin and pioglitazone but inferior to GLP-1 RA. DPP4i require dose reduction with renal impairment except linagliptin. There has been concerns of risk of pancreatitis and pancreatic cancer. There has also been a warning issued by the US FDA about the possibility of joint pains developing during the treatment. They have a neutral effect on the cardiovascular outcomes. An increase in the hospitalization due to Saxagliptin was shown in SAVOR-TIMI trial but there was no increase in the mortality.

GLP-1 RA:-

GLP-1 RA are either analogs of human GLP-1 (liraglutide, dulaglutide, albiglutide) or are based on the exendin molecule (exenatide, lexisenatide). Clinical trials have shown that the GLP-1 RA effectively lower the blood glucose levels when used as a monotherapy or in combination with other drugs. The HbA1c reduction ranges from 0.8 to 1.5%. They have low intrinsic risk of causing hypoglycaemia due to the "glucose dependence" of their insulin secretory effect. GLP-1 RA induce satiety and produce a mean weight loss of about 3 kgs. GLP-1 RA also inhibit glucagon secretion which suppresses the hepatic glucose production. These effects lead to superior glycaemic efficacy compared with the DPP4i. The main adverse effect is nausea. There is a small increased risk of pancreatitis. Other concerns are regarding the C-cell thyroid tumours. GLP-1 RA also cause a fall in the systolic blood pressure of 2-3 mm Hg and a 2-3 beats per minute increae in heart rate. They have a neutral effect on cardiovascular outcomes.

SGLT-2 inhibitors:-

Under physiologic conditions, SGLT-2 transporter in the renal proximal tubule reabsorbs 80-90% of the filtered glucose. SGLT-2 is primarily expressed in the kidney, but is also found in the α-cells. Three SGLT-2 inhibitors are approved worldwide i.e. Canagliflozin, Dapagliflozin and Empagliflozin. SGLT-2 inhibitors are given once daily with a HbA1c reduction of 0.6-1.0% in individual trials. They can be used as a monotherapy or as dual or triple therapy with other OHAs or with insulin. They are effective in individuals with type 2 DM with eGFR of >45-60 ml/min/1.73 m^2BSA. SGLT-2 inhibitors also produce a weight loss of about 2-3 kgs secondary to the 280-320 kcal/ day that is lost as glucose (70-80 gms) (each gm of glucose is equal to 4 kcal) in the urine. SGLT-2 inhibitors also cause a reduction of blood pressure of systolic 3-6 mm Hg and the diastolic 1-2 mm Hg.

The main adverse effects are the 4-5 fold rise in the risk of genital fungal infections and a small increase in bacterial urinary tract infections. Volume depletion can be a problem particularly in the elderly. Some trials have reported episodes of diabetic ketoacidosis in patients of type 2 and type 1 taking these drugs. This is due to the shift in the substrate metabolism from glucose to fatty acid oxidation and the promotion of hyperglucagonemia which stimulates ketogenesis. Ketoacidosis may also be associated with insulin dose reductionand stress. Some of the SGLT-2 inhibitors are associated with an increased risk of bone fractures, especially Canagliflozin. This may be due to increase in phosphate, PTH and FGF-23 concentration and small decreases in Sr 1,25-$(OH)_2$ Vit D levels. The volume depletion may predispose to falls in the elderly. GLP-1 RA have been shown to have superior glycaemic efficacy and better beneficial affects on body weight as compared to DPP4i. They have not been compared with SGLT-2 inhibitors in trials.[2]

Current Guidelines:-

HbA1c should be reduced to as near normal as possible. Metformin still remains the first choice after lifestyle modification in most guidelines. The latest National Institute for Health and Care Excellence (NICE) Guidelines recommend the use of metformin as the initial choice of therapy and a target HbA1c of <6.5% most patients. For intensification of drug therapy, it is recommended to consider metformin and a DPP4i or pioglitazone or a sulphonylurea or SGLT-2 inhibitor aming for a glycaemic target of <7%. For the second intensification, triple therapy with following are recommended-

1) Metformin, DPP4i, Sulphonylurea,
2) Metformin, Pioglitazone, Sulphonylurea,
3) Metformin, Pioglitazone/ Sulphonylurea, SGLT-2 inhibitor.

Insulin is also recommended at this stage.

If metformin is contraindicated or not tolerated, then DPP4i or pioglitazone or sulphonylurea is recommended as the initial therapy, followed by combination of DPP4i and pioglitazone, DPP4i and sulphonylurea or pioglitazone and sulphonylurea. Insulin is to be considered for second intensification.

NICE recommends that GLP-1 RA to be considered in type 2 DM patient with a BMI of >35 kg/m^2 BSA. Continuation of GLP-1 RA therapy is recommended if ≥1% reduction in HbA1c and ≥3% weight loss are achieved in 6 months.

The NICE approach is based on cost effectiveness. The guidelines are

flexible with respect to addition of a third agent if adequate glycaemic control is not achieved and basal recommended insulin if target HbA1c is not achieved for 3 months.

In all the guidelines, metformin remains the first drug of choice. For patients who do not achieve individualized HbA1c target with metformin monotherapy, the individualized treatment approach can include choosing the second optiondrug based upon the patient preferences, effect on the body weight, hypoglycaemia risk, cardiovascular risk/benefit, durability of glycaemic control, ability to correct the known pathophysiological abnormality, prevention of progressive B-cell destruction and the side effects.[3]

In conclusion, it can be said that SGLT-2 inhibitors and incretin based therapies are the relatively new treatments for type 2 DM. These agents should be used early in the natural history of type 2 DM because of their attributes.

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