MEDIBEATS
The Medical Bulletin

In Diabetes

TIRZEPATIDE: TWINCRETIN CONCEPT ON THE WAY TO TREAT DIABESITY

TIRZEPATIDE, A NOVEL DUAL GIP/GLP-1 RECEPTOR AGONIST (TWINCRETIN), HAS BEEN FORMULATED AS A SYNTHETIC PEPTIDE CONTAINING 39-AMINO ACIDS, BASED ON THE NATIVE GIP. TIRZEPATIDE HAS A COMPARABLE GIP RECEPTOR BINDING AFFINITY TO NATIVE GIP AND FIVE TIMES LOWER GLP-1 RECEPTOR AFFINITY THAN THAT OF NATIVE GLP-1. THE CLINICAL EFFICACY, TOLERABILITY, AND SAFETY OF TIRZEPATIDE HAVE BEEN REPORTED IN DIFFERENT RANDOMIZED CONTROLLED TRIALS (RCTS).

GLUCOSE-DEPENDENT INSULINOTROPIC PEPTIDE (GIP) IS FOUR AMINO ACID INCRETIN PEPTIDE, PRODUCED BY K-CELLS OF DUODENUM AND PROXIMAL JEJUNUM, RELEASED IN RESPONSE TO ORAL CARBOHYDRATES AND LIPID LOAD, HAVING SHORT HALF-LIFE OF 4–7 MIN AND INACTIVATED BY DIPEPTIDYL PEPTIDASE (DPP)-4 ENZYME. GIP RECEPTORS HAVE BEEN DOCUMENTED IN HEART, PANCREAS, GASTRIC MUCOSA, ADIPOSE TISSUE, BONE, ADRENAL CORTEX, AND BRAIN. UNLIKE GLP-1, GIP HAS GLUCAGONOSTATIC IN THE HYPERGLYCEMIC STATE, BUT GLUCAGONOTROPIC PROPERTY DURING NORMOGLYCEMIC AND HYPOGLYCEMIC STATE.

GLUCAGON IS KNOWN TO PREVENT HYPOGLYCEMIA. HENCE, THIS GLUCAGONOTROPIC PROPERTY IN HYPOGLYCEMIC STATES MAKES GIP-BASED THERAPY FOR TYPE-2 DIABETES (T2DM) REALLY ATTRACTIVE DUE TO THE LOWER RISK OF HYPOGLYCEMIA.

T2DM IS CHARACTERIZED BY LOSS OF INSULINOTROPIC PROPERTY OF GIP ALONG WITH LOSS OF GLUCAGONOSTATIC IN THE HYPERGLYCEMIC STATE (GIP RESISTANCE).

HOJBERG ET AL DEMONSTRATED THAT SUPRAPHYSIOLOGIC EXOGENOUS GIP ADMINISTRATION IN PEOPLE WITH T2DM INCREASED THE INSULIN RESPONSE (INCRETIN EFFECT), PARTLY RESTORING INSULINOTROPIC PROPERTIES. PHYSIOLOGIC STUDIES HAVE DEMONSTRATED THAT COINFUSION OF GLUCAGON-LIKE PEPTIDE (GLP)-1 AND GIP HAS A SYNERGETIC EFFECT RESULTING IN SIGNIFICANTLY INCREASED INSULIN RESPONSE AND GLUCAGONOSTATIC RESPONSE RESULTING IN A SIGNIFICANT LOWERING OF BLOOD GLUCOSE, AS COMPARED TO THE SEPARATE ADMINISTRATION OF EACH OF THE HORMONE IN T2DM.

IN VARIOUS PHASE 3 META ANALYSIS, TIRZEPATIDE AT 10 MG/12 MG PER WEEK WAS FOUND TO BE SUPERIOR TO DULAGLUTIDE, SEMAGLUTIDE, DEGLUDEC, AND GLARGINE INSULIN WITH REGARDS TO GLYCEMIC EFFICACY (HBA1C, FPG, PPG REDUCTION, AND PERCENTAGE OF PATIENTS ACHIEVING HBA1C <7, <6.5, AND <5.7%) AS WELL AS REDUCTION IN OBESITY (BODY WEIGHT, BMI, WAIST CIRCUMFERENCE REDUCTION, PERCENTAGE OF PEOPLE ACHIEVING >5, 10%, AND 15% WEIGHT LOSS). THESE RESULTS SUGGEST THAT TIRZEPATIDE MAY BE THE MOST POTENT AGENT DEVELOPED TILL DATE TO TACKLE DIABESITY.

MEDIBEATS
The Medical Bulletin

TIRZEPATIDE IS AN IMBALANCED DUAL AGONIST IN FAVOR OF GIPR OVER GLP-1R ACTIVITY. IT SHOWS EQUAL AFFINITY FOR THE GIPR COMPARED WITH NATIVE GIP BUT BINDS THE GLP-1R WITH APPROXIMATELY 5-FOLD WEAKER AFFINITY THAN NATIVE GLP-1. THIS IMBALANCED ACTIVITY OF THIS NOVEL MULTIINCRETIN MAY EXPLAIN THE UNPRECEDENTED IMPACT ON GLYCEMIC CONTROL, WEIGHT LOSS, AND OTHER PLEOTROPIC BENEFITS OF TIRZEPATIDE.

PATIENTS RECEIVING TIRZEPATIDE HAVE INCREASED OCCURRENCE OF TREATMENT EMERGENT SIDE EFFECTS BOTH COMPARED TO ACTIVE CONTROLS AND PLACEBO CONTROLS. THE OCCURRENCES OF SAES WERE NOT DIFFERENT WITH TIRZEPATIDE AS COMPARED TO ACTIVE OR PLACEBO CONTROLS. GASTROINTESTINAL SIDE EFFECTS WERE PREDOMINANT TYPE OF SIDE EFFECTS NOTED WITH TIRZEPATIDE, WHICH IS SIMILAR TO GLP-1R ANALOGUES. IT HAS BEEN SUGGESTED IN SOME STUDIES THAT THE SIGNIFICANTLY LOWER GLP-1R AFFINITY OF TIRZEPATIDE AS COMPARED TO THE GLP-1R ANALOGUES DULAGLUTIDE OR SEMAGLUTIDE MAY EXPLAIN MARGINALLY LOWER GASTROINTESTINAL SIDE EFFECTS WITH THIS MOLECULE. THE REPORTED ANTIEMETIC EFFECT OF GIP AGONISM MAY ALSO CONTRIBUTE TO THE BETTER GASTROINTESTINAL TOLERABILITY OF TIRZEPATIDE.

TIRZEPATIDE IS A WELCOME ARMAMENTARIUM IN THE WAR AGAINST DIABESITY AND SHOULD HELP IN DIABETES REVERSAL IN THE REAL-WORLD SCENARIO. THE SIDE-EFFECT PROFILE ESPECIALLY GASTROINTESTINAL TOLERANCE AND MONTHLY COST OF THERAPY WOULD HAVE AN IMPORTANT IMPACT ON THE ACCEPTABILITY OF THIS MOLECULE IN CLINICAL PRACTICE, ESPECIALLY IN THE DEVELOPING WORLD.

Dr. Minal Mohit