Hellenic Diabetological Chronicles 31, 2: 110-111, 2018

Incretin based therapies – novelties to learn 2018

Baptist Gallwitz

Prof. Dr. med., Internal Medicine, Deputy head of the Department for Endocrinology, Diabetes and Metabolism at the University of Tübingen, Past President of the German Diabetes Association, Germany

Incretin based therapies comprising the orally active dipeptidyl peptidase-4 inhibitors (DPP-4i) and the injectable glucagon-like peptide-1 receptor agonists (GLP-1RA) have been introduced into type 2 diabetes therapy twelve years ago. They utilize the action of the hormone GLP-1 that stimulates insulin secretion and inhibits glucagon secretion in a plasma glucose-dependent manner. DPP-4i inhibit the ubiquitous enzyme DPP-4 that physiologically degrades and inactivates GLP-1 as main substrate and therefore elevate endogenous GLP-1 plasma concentrations appr. 3-fold. GLP-1RA lead to an 8-10-fold elevation.

DPP-4i have a very low hypoglycaemia risk and are body weight neutral. In many comparative studies they have shown similar efficacy as sulfonylureas. Cardiovascular safety studies have demonstrated cardiovascular safety regarding a composite primary endpoint consisting of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke. DPP-4i are mostly used as second line oral medication after metformin failure in a combination with metformin. Fixed dose combinations for metformin and DPPi are available. In patients with metformin intolerance or metformin contraindications (e.g. renal failure) they are also often used in monotherapy.

GLP-1RA also have a very low hypoglycemia risk. They allow body weight loss that is explained by two mechanisms: 1) GLP-1 acts as a mediator of satiety in the central nervous system and 2) slows gastrointestinal motility facilitating the sensation of fullness (and nausea as adverse event). GLP-1RA are also mainly used after metformin failure, mostly in patiens with obesity when body weight loss is another important treatment goal. Short acting (for daily dosing) or long acting (for once weekly dosing) substances can be used. One GLP-1RA has also received approval for the treatment of obesity independently of type 2 diabetes. Two long acting GLP-1RA have shown superiority regarding cardiovascular outcomes in comparison to standard antidiabetic treatment. GLP-1RA have also a beneficial potential in the use of a combination therapy with insulin treatment. This combination is often less complex than an insified insulin regimen, leads to less hypoglycaemic episodes and is more favorable regarding the body weight gain observed during insulin therapy.

A review of both substance classes, the DPP-4i and GLP-1RA

is given regarding their present usage and placement in the treatment guidelines for type 2 diabetes. Their potential in combination therapies is presented, especially in later stages of type 2 diabetes in combination with insulin or with SGLT-2 inhibitors. Furthermore, novel data that open up potential novel indications and treatment options are presented. For DPP-4i this includes an overview on other substrates for DPP-4 besides GLP-1 and the potential consecutive clinical implications arising. For the GLP-1RA novel forms of applications are introduced.