Incretin based Therapy

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Physiology of the incretin system

The gut secretes few hormones in response to food intake, of which glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) are the most important in terms of glucose regulation. GLP-1 and GIP are collectively termed "the incretin hormones," and they directly influence the pancreas. They both stimulate pancreatic β-cells to release insulin in response to glucose, and GLP-1 also suppresses postprandial glucagon output. The actions of these hormones is to limit rises in postprandial blood glucose, and in their absence, the pancreatic response to glucose is reduced. This "incretin effect," was described after observations that equivalent plasma glucose concentrations elicited greater insulin release when ingested than when delivered via intravenous infusion. This incretin effect is diminished in type 2 diabetes and pharmacotherapies targeting this system are quite effective.

Because of reduced pancreatic response to GIP this hormone was not initially considered a candidate for drug development, but GLP-1 was studied since it showed the ability to reduce hyperglycemia in type 2 diabetes when infused at supraphysiological levels.

Native GLP-1 is rapidly degraded by the enzyme dipeptidyl-peptidase (DPP)-4. This enzyme, expressed in many tissues, rapidly cleaves the incretins. As a result, native GLP-1 persists in the circulation for few minutes. As such human GLP-1 cannot be readily used clinically since it would need to be given by continuous infusion. As a result, GLP-1 analogs that were resistant to DPP-4 or drugs that could maximize the effects of endogenous GLP-1 by inhibiting DPP-4 were developed.

The use of a GLP-1 receptor agonist (GLP-1 RA) and a DPP-4 inhibitor (DPP-4i) in patients with type 2 diabetes has been approved for both monotherapy and combination therapy approaches.

DPP-4i

There are also several DPP-4i drugs, these include sitagliptin, vildagliptin, alogliptin, linagliptin and saxagliptin. They are administered orally and typically require once-daily or twice daily dosing independent of food intake. DPP-4i confers a 2 to 3 fold increase in postprandial plasma concentrations of endogenous GLP-1, thereby reducing postprandial hyperglycemia.

GLP-1 RA

Exenatide, liraglutide, lixisenatide, dulaglutide, semaglutide are GLP-1 agonists currently available. Exenatide is a synthetic version of exendin-4 (a salivary gland peptide from the Gila monster lizard), which has an amino acid sequence similar to that of human GLP-1. liraglutide, lixisanatide, dulaglutide, semaglutides are analogs of human GLP-1 with a primary amino acid sequence that is nearly identical (to that of human GLP-1. They administered by subcutaneous injection in the thigh, abdomen, or upper arm and are available in prefilled multi-dose pens to be used either daily or weekly.

Side effects

Hypoglycemia is uncommon with both GLP-1 RAs and DPP-4 is, and trial data indicate that it is most commonly reported in patients taking concomitant Sulfonylureas (SUs). The most commonly reported side effect of GLP-1 use is nausea. This is usually transient and typically resolves after the first month.

There has been concern about an increased risk of pancreatic effects with incretin-related therapies. However, because patients with type 2 diabetes have a 2.8-fold higher risk than the general population of developing pancreatitis, it has not been established whether the association between pancreatitis and incretins is causal or artifactual. Nevertheless, there have been reports of acute pancreatitis in patients receiving DPP-4i and GLP-1RA.

Thyroid C-cell tumors have been associated with GLP-1 RA in rodents. GLP-1 RAs are localized to rodent C-cells, and application of GLP-1 RAs stimulated calcitonin release, upregulation of calcitonin gene expression, and C-cell hyperplasia in rat and mouse models. However, GLP-1 receptor expression in C-cells is comparatively low in humans and other primates. GLP-1 RAs are contraindicated in patients who have a history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2.

A potential safety concern with DPP-4 inhibitors is the possibility that these agents may cause extremely rare hypersensitivity and allergic reactions. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions such as Stevens-Johnson syndrome and require immediate discontinuation of treatment.

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Indications for Incretin-Related Therapies

The glucose-lowering effects of GLP-1 RAs and DPP-4 is make incretin-related therapies well suited to patients with poor glycemic control. A key benefit of incretin-related therapies is that, similar to the SUs, they have the potential to increase insulin secretion but, unlike SUs, incretin-mediated insulin secretion (as well as inhibition of glucagon secretion) is glucose dependent. As such, incretin-stimulated insulin secretion only operates under hyperglycemic conditions, resulting in an inherently low risk of hypoglycemia. Incretin-related therapies therefore have a clear clinical utility in patients such as the elderly, who are at high risk of, or at extra risk from, hypoglycemia.

GLP-1 also slows gastric motility, promotes satiety and reduce appetite even in fasting individuals. In clinical trials, GLP-1 RA effects translated into significant weight loss in diabetes patients and in obese non-diabetic individuals.

Incretin-related therapies also promise therapeutic benefits with regard to the cardiovascular system. Effects have been demonstrated with GLP-1 and GLP-1RAs, including reductions in systolic blood pressure, inflammatory markers of CVD (such as PAI-1 and BNP), and improved vasodilatory function.

Few studies have directly compared GLP-1 RAs with DPP-4 is, but available evidence suggests that GLP-1 RAs are more effective glucose-lowering therapies and have the additional advantages of weight and systolic blood pressure reduction. DPP-4i has the advantage of oral administration and excellent tolerability. The best results are obtained when these agents are used in combination with metformin.

Cardiovascular outcome trials:

The FDA in the US and the EMA in Europe have required new drugs for the treatment of diabetes to demonstrate cardiovascular safety, usually including a double-blind placebo-controlled cardiovascular outcome trial (CVOT). The focus on safety has been particularly on atherosclerotic outcomes, so the primary end point required for the FDA was either the composite end point of major cardiovascular events (MACE), a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke, or MACE plus, with the addition of hospitalization for unstable angina.

We now have multiple completed CVOTs for the drug classes of DPP-4 is and GLP-1 RAs.

DPP-4 inhibitor CVOTs

SAVOR-TIMI 53 involved 16,492 patients with type 2 diabetes and established atherosclerotic CVD or multiple risk factors for vascular disease who were followed for a median of 2.1 years. The results: No significant difference in MACE comparing saxagliptin and placebo. A statistically significant increase in HFH in the saxagliptin group.

EXAMINE involved 5,380 patients with type 2 diabetes and an acute coronary syndrome (acute myocardial infarction [MI] or unstable angina requiring hospitalization). Treatment was started within 15 to 90 days of the acute coronary syndrome (ACS) for a median duration of 18 months. The results: No significant difference in MACE comparing alogliptin and placebo.

TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) was a trial comparing sitagliptin and placebo in 14,671 subjects with a median follow-up of three years. The results: There was no difference in the primary outcome, which was MACE plus hospitalization for unstable angina, or in MACE which was a secondary outcome.

CARMELINA (Cardiovascular and Renal Microvascular Outcome Study with Linagliptin) included 6,991 patients with established atherosclerotic CVD plus macroalbuminuria, or patients with impaired renal function and/or albuminuria. The results: There was no significant difference in MACE, MACE plus or HFH comparing linagliptin and and placebo. There was no difference in a renal composite outcome of death due to renal failure, end stage renal disease or a decrease in eGFR of 40% or more comparing linagliptin and placebo.

CAROLINA (Cardiovascular Outcome Study of Linagliptin vs. Glimepiride in Type 2 Diabetes) compared linagliptin with the sulfonylurea glimepiride in 6,042 patients with established atherosclerotic CVD or increased cardiovascular risk. The results: There was no significant difference in MACE, MACE plus or HFH comparing linagliptin and and glimepiride,

GLP-1 receptor agonist CVOTs

ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome) with lixisenatide. 6,068 patients with type 2 diabetes and a recent ACS with a median follow-up period of 25 months. Participants were diagnosed with ACS, defined as MI (ST elevation or non-ST elevation) or hospitalization for unstable angina, in the 180 days preceding randomization. The results: No significant difference in MACE comparing lixisenatide and placebo

LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) included 9,340 patients with established CVD or cardiovascular risk who were randomized to receive liraglutide (1.8 mg once daily or maximum tolerated dose) or placebo with median follow-up of 3.8 years. The results: The primary MACE end point occurred in significantly fewer patients in the liraglutide group than in the placebo group (13% *vs*. 14.9%; HR 0.87; 95% CI 0.78 to 0.97; $p<0.001$ for noninferiority, $p=0.01$ for superiority).

SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes). 3,297 patients with type 2 diabetes were randomized to receive once weekly semaglutide (0.5 mg or 1 mg) or placebo in a 1:1:1 ratio for 104 weeks. Patients had established CVD, chronic kidney disease, or both, or raised cardiovascular risk. The rsults:The primary MACE outcome occurred in 108 (6.6%) patients treated with semaglutide compared with 146 (8.9%) patients treated with placebo (HR 0.74; 95% CI 0.58 to 0.95; $p<0.001$ for noninferiority, $p=0.02$ for superiority).

EXCEL (Exenatide Study of Cardiovascular Event Lowering Trial) was a large study, which randomized 14,752 patients to receive extended-release exenatide or placebo once weekly with a median of 3.2 years follow-up. The results: The primary outcome of MACE occurred in similar numbers of patients in the exenatide and placebo groups (11.4% *vs*. 12.2%; HR 0.91; 95% CI 0.83 to 1.00; $p<0.001$ for non-inferiority, $p=0.061$ for superiority).

REWIND (Researching Cardiovascular Outcomes with a Weekly Incretin in Diabetes) was different from earlier CVOTs with GLP-1 receptor agonists as the majority of subjects were recruited because of increased cardiovascular risk (69%) and the minority (31%) had a history of CVD. The results:

MACE was significantly reduced in the dulaglutide group (HR 0.88; 95% CI 0.79 to 0.99; p=0.026). The result was driven primarily by a reduction in nonfatal stokes.
Thus, several GLP-1 RAs have demonstrated reductions in atherosclerotic cardiovascular events and in proteinuria, with minimal if any reductions in hospitalization for heart failure.

American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) guidelines:

DPP-4 is are currently widely used as a treatment for type 2 diabetes and most commonly initiated after metformin. They have few side effects and are are quite efficacious. However, the lack of any cardiovascular harm means that these drugs can be used in patients were avoidance of weight gain or avoidance of hypoglycemia is the main clinical issue.
The ADA and EASD recommend the use of GLP-1 RAs to reduce the risk of MACE in patients with type 2 diabetes and established atherosclerotic CVD (such as prior MI, unstable angina, coronary revascularization) as the level of evidence for MACE benefit is greater than for SGLT2 inhibitors. Cardiologists should consider the initiation of a GLP-1 receptor agonist when these patients are consulted in outpatients, admitted to hospital, or attend for cardiac rehabilitation.
Within the GLP-1 receptor class, clear cardiovascular benefits have been demonstrated with liraglutide, semaglutide and dulaglutide, with less certain benefit from oral semaglutide and once-weekly exenatide, and no demonstrable benefit from lixisenatide.

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