

New GLP-1 Analog in Type 2 Diabetes

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ABSTRACT

Oral Semaglutide, an investigational GLP-1 analog for type 2 diabetes, achieved its primary end point in Phase 3a trial. The trial compared a once-daily tablet of oral Semaglutide with placebo in patients with type 2 diabetes uncontrolled with diet and exercise alone. The highest dose also significantly reduced body weight, a secondary end point.

Taken as a whole, the results released are consistent with the clinical profile of injectable GLP-1 receptor agonist therapy, thus far suggesting high glycemic efficacy and ability to achieve glycemic goals, with low risk of hypoglycemia and additional benefit of weight loss.

Introduction

Type 2 diabetes mellitus is a complex, progressive disease affecting an estimated 425 million people between the ages of 20 and 79, and that type 2 diabetes comprise about 90% of these cases. A number of unmet needs are present with traditional T2DM therapies, which can lead to insufficient glucose control and increased risk of diabetic complications.¹

Metformin has remained the first-line treatment for type 2 diabetes. Other therapeutic options to manage glucose levels include insulin, sulphonylureas, and thiazolidinediones.² However, maintaining glucose homeostasis with these drugs remains challenging for many patients.³ Furthermore, some of these drugs particularly insulin and sulfonylureas lead to undesired risks including hypoglycemia and weight gain. Thus, identifying new drugs and developing more effective and safer treatments is necessary to achieve optimal management of type 2 diabetes.⁴

An emerging class of diabetes therapeutics, the glucagon-like peptide-1 receptor agonists (GLP-1 RAs), seems to address many of the unmet needs of individuals with T2DM. This review summarises the recent findings and current clinical guidelines of

the currently approved GLP-1 receptor agonists and explores the new GLP-1 receptor agonists in development. It also concentrates on the physiological basis for early use of GLP-1 receptor agonists, their use as an alternative to insulin therapy, the rationale for combining them with insulin and their cost-effectiveness.

GLP-1 is an incretin hormone secreted by L-cells in the distal small bowel and colon. GLP-1 is released in response to food absorption in the gut and helps to stimulate insulin secretion in the pancreatic b-cells, while also suppressing glucagon secretion. The action of the incretin hormones - GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) account for up to 60% of insulin secretion after oral glucose intake.⁵

Effects of GLP-1 RA delivery strategies on drug efficacy and safety

Different modification approaches not only affect the pharmacokinetic profiles of GLP-1 RAs but also strongly influence their efficacy, safety profile and usability. The main pharmacological efficacy biomarkers determined in Phase 3 studies for GLP-1 RAs are based on the pharmacokinetic properties, GLP-1 RAs could be roughly divided into short-acting agonists which are administered once or twice daily, and long-acting agonists which are administered once weekly. The two groups of GLP-1 RAs, while sharing many similarities, present different pharmacodynamic features and, thus yield different anti diabetic efficacy.

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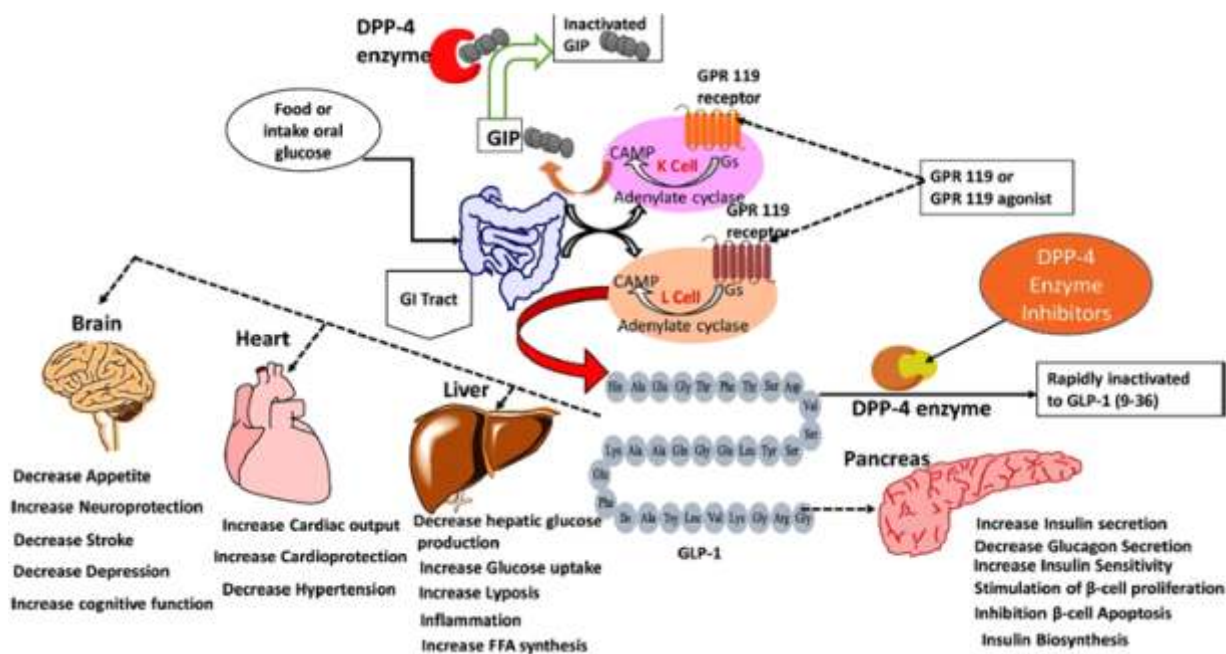
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GLP-1 Synthesis, Release, Metabolism & Effects of GLP-1 on body organs⁵



Biological actions of GLP-1 and pathophysiology in diabetes and obesity

Major effect of GLP-1 are related to glucose metabolism, increasing pancreatic β -cell insulin secretion (in a glucose dependent manner) and inhibiting hepatic glucose production via reduced α -cell glucagon secretion. A uniformly reduced incretin effect is seen in individuals with type 2 diabetes and obesity with reduced GLP-1 levels in the majority.⁶ Pancreas remains responsive to GLP-1 but is no longer responsive to glucose-dependent insulinotropic polypeptide (GIP), which is the most likely reason for a reduced or absent incretin effect. Subsequently GLP-1 RAs have been a significant development in the pharmacological management of type 2 diabetes. Furthermore, GLP-1 upregulates the expression of glucokinase and glucose transporter genes involved in glucose metabolism and transport, improving whole body glucose disposal and insulin resistance.⁶⁻⁸ A significant reduction in β -cell volume is demonstrated in obese individuals with type 2 diabetes (63%) or pre-diabetes (40%) compared to healthy obese controls.⁹ Animal studies have suggested that GLP-1 and GIP can increase β -cell mass (regeneration and reduced apoptosis)¹⁰ with findings of a small (n=69) clinical

study in type 2 diabetes demonstrating preservation of β -cell function after 3 years of treatment with a short-acting GLP-1 RA.¹¹⁻¹³

GLP-1 Analog for Type 2 Diabetes

In patients with type 2 diabetes, the class of drugs called glucagon-like peptide 1 (GLP-1) receptor agonists are highly effective for blood glucose control. They also help to reduce weight, and some may provide cardiovascular benefits. However, they're currently only available in injectable form, which is known to be a barrier for some patients and providers.¹²

Oral version may be on the horizon.

Oral semaglutide, an investigational GLP-1 analog for type 2 diabetes, achieved its primary end point in the PIONEER 1 Phase 3a trial, according to data presented at the American Diabetes Association's Scientific Sessions in June 2017. The trial compared a once-daily tablet of oral Semaglutide (3, 7, and 14 mg) with placebo in patients with type 2 diabetes uncontrolled with diet and exercise alone. All 3 doses significantly reduced HemoglobinA1c compared with placebo by 26 weeks. The highest dose also significantly reduced body weight, a secondary end point. As part of its PIONEER

program, investigators are also evaluating oral semaglutide in 9 other phase 3a trials comparing the investigational therapy with available antidiabetic agents. Results have been announced for 4 of those trials, with the remainder expected before the end of 2018.

Taken as a whole, the results released are consistent with the clinical profile of injectable GLP-1 receptor agonist therapy, thus far suggesting high glycemic efficacy and ability to achieve glycemic goals, with low risk of hypoglycemia and additional benefit of weight loss is seen.

Investigators plans to submit oral semaglutide for regulatory approval in 2019, according to a company spokesperson. The US Food and Drug Administration approved semaglutide injection (Ozempic) for type 2 diabetes in December, 2017. Meanwhile, the quest for oral insulin is also advancing. A recent preclinical study reported that a novel oral insulin formulation decreased blood glucose by 45% over 10 hours.¹⁴

Barriers to Oral Glucagon-Like Peptide-1 and Glucagon-Like Peptide-1 Analog Delivery

As a gatekeeper of the human body, the GI tract has several barriers that thwart drugs from being absorbed. It provides an optimum environment for the entry of nutrients and for digestion but is a hostile environment to pathogens and xenobiotics, making the absorption of oral-active drugs a real challenge. The variable pH along the GI tract (pH ranging from 13 to 6.58) is the first impasse to peptide absorption. This variation induces several modifications on peptides that can lead to the loss of their conformation or even to their partial destruction

before reaching the intestine. Another main risk for GLP-1 and its analogs absorption is their rapid degradation by enzymes secreted throughout the GI lumen, like pepsine, pancreatic enzymes, and peptidases and enzymes from the intestinal flora.¹⁵

Discussion :

With the rising prevalence of obesity and associated type 2 diabetes attention has rightly been directed towards treatment strategies that promote weight loss. GLP-1 RAs have become a successful treatment for type 2 diabetes and obesity with effective glucose control and modest weight loss. Their potential cardiovascular benefits are also receiving increasing focus and may lead to use earlier in the disease process, atleast for those with pre-existing cardio vascular disease. Despite their success, even with the development of longer-acting agents, we still see heterogeneity in response to treatment, both in terms of weight loss and HbA1c reduction. This may reflect a number of factors e.g. pharmacokinetics, that results in different drug exposure at the same dose (e.g. depending on body size), or other patient factors (biological and non-biological) that might alter response. There have been some small advances in this area with studies attempting to explain the heterogeneity, particularly weight change, by stratification of weight loss: 'responders' (who have lost = 5% of their initial body weight) and 'nonresponders' (who have lost = 5% of their initial body weight). It is perhaps not surprising that early response to a weight loss intervention can predict long-term weight loss. The future in obesity and type 2 diabetes management clearly involves combination treatments that mimic

Table 1 : Clinical status of GLP-1 agonists

no	Drug	Dose	USFDA	EMA	PHASE 3
1	Dulaglutide Trulicity	0.75 or 1.5 mg	18 Sep 14	25 Nov 14	AWARD
2	Semaglutide	0.5 mg or 1.5 mg/week	18 Oct 17	2 Dec 16	SUSTAIN
3	Efpeglenatide	8 mg	Yet to be approved	Yet to be approved	–
4	Itca 650	20 mcg, 40 mcg	Rejected	Yet to be approved	FREEDOM

the benefits of bariatric surgery with glycaemic benefit, control of appetite and weight loss. The hope is that the combination of gut hormone analogues will have additive or even synergistic effects in improving glycaemic control and reducing caloric intake and subsequently weight loss. At present we are some way off from this reality with only a few examples of novel peptide co-agonists demonstrating proof of concept. It does however seem highly likely that the next decade will deliver significant advances in combination therapies for obesity and associated type 2 diabetes.¹⁶⁻¹⁷

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