Semaglutide seems to be more effective the other GLP-1Ras

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Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) were introduced as treatment options for type 2 diabetes (T2DM) in 2005 (1). They have become popular because of their efficacy and durability in relation to glycaemic control, and their low risk of hypoglycaemia in combination with weight loss in most patients (2,3).

GLP-1 RAs mimic the effects of native GLP-1, including potentiation of glucose-induced insulin secretion, inhibition of glucagon secretion, inhibition of gastric emptying and inhibition of appetite and food intake (2,3). Notably, the insulinotropic and glucagonostatic effects are glucose dependent, meaning that insulin secretion is only stimulated at euglycaemic or elevated glucose concentrations, while hypoglycaemia-induced glucagon secretion surprisingly is not inhibited. Therefore, the risk of hypoglycaemia is very low during treatment with a GLP-1 RA, unless it is combined with sulfonylureas or insulin (2-4).

The GLP-1 RAs fall into two categories, the short acting and the long acting agonists. Today the former only include agents identical to (Exenatide) or derived from (Lixisenatide) the Gila Monster salivary peptide, exendin 4 (5). With their subcutaneous half-lives of 2–3 hours, their effect wears off rapidly and mainly covers a single meal. It turns out that the effect on gastric emptying is primarily observed with the short acting GLP-1 RAs, since significant tachyphylaxis for this effect develops, within hours, upon continued exposure with a GLP-1 agonist, and the effect is nearly gone after few days' treatment with the long acting GLP-1 RAs (6,7). The explanation for this and for the absence of tachyphylaxis regarding the metabolic effects remains unknown. In addition, GLP-1 RAs reduce blood pressure during chronic treatment and increase pulse rate, both by still unknown mechanisms. The agonists also appear to reduce postprandial triglyceride concentrations (8-10) by an effect that appears to be independent of the effects on gastric emptying, but may reflect inhibition of chylomicron formation (11). Agonist treatment does not lead to fat malabsorption, though.

GLP-1 has repeatedly been reported to exert protective effects on the beta cells, originally by promoting beta-cell proliferation (which may only apply to young beta cells) and inhibition of cytokine- and FFA-induced apoptosis (12). This effect might be expected to reduce or halt the progression of type 2 diabetes, but the findings in this regard are unclear (13). In one study, beta cell function was evaluated after three years of treatment with high doses of a short acting GLP-1 RA (exenatide), and during this period there was no deterioration, but the same was true in the control group subjected to intensive insulin therapy (14), suggesting that both approaches may be protective. In the LEADER study of the cardiovascular safety of the long-acting GLP-1 RA, liraglutide, hemoglobin A1c levels remained almost unchanged over a period of up to 5 years without changes in the liraglutide dosing and in spite of significantly lesser increases in concomitant antidiabetic medications than in the placebo group. Since beta cell function would otherwise be expected to deteriorate significantly in a period of this duration, the finding is likely

to reflect some protective action on the beta cells, although the nature of this remains unclear (15).

Studies in rodent models of Parkinson's and Alzheimer's diseases and mouse models of ischaemic stroke have suggested that GLP-1 receptor agonist might have neuroprotective effects and prevent memory impairment (16-18). However, studies in humans have not supported the use of GLP-1 RA in cerebral diseases (19), except for one clinical trial of 48 weeks, which suggested that exenatide once weekly had positive effects in Parkinson's disease, which were sustained beyond the period of exposure (20). Whether the exenatide therapy affects the underlying disease pathophysiology or the result simply is secondary to long-lasting metabolic improvements is uncertain.

Apart from these actions, the GLP-1 RAs may also have protective cardiovascular effects and recently, three cardiovascular outcomes studies, showing beneficial effects of GLP-1 RAs on cardiovascular risk in patients with type 2 diabetes and heart problems have appeared (15,21,22). These results are likely to further support the enthusiasm for these agents.

The most common adverse events of The GLP-1 RAs are nausea and other gastrointestinal discomfort (2,3) which are usually mild to moderate and usually subside after a few weeks. A slow up-titration schedule often prevents most of the nausea. Other drawbacks of the GLP-1 RAs include the parenteral administration and the cost (2).

As a drug class, the GLP-1RAs have proven efficacy for lowering HbA1c and decreasing weight in T2D, with a reduced risk of hypoglycaemia compared with insulin or sulphonylureas (1,2,23). These characteristics underlie the inclusion of GLP-1RAs in various clinical practice guidelines. Their use as dual therapy with metformin after first-line metformin and as triple therapy (in combination with metformin and a sulphonylurea/thiazolidinedione/insulin) is part of the European Association for the Study of Diabetes/American Diabetes Association recommendations (1). GLP-1 RAs are recommended as monotherapy, dual therapy and triple therapy by the American Association of Clinical Endocrinologists/American College of Endocrinology guidelines (23).

Semaglutide once weekly

Liraglutide is a long-acting GLP-1 RA developed by NovoNordisk from the backbone of human (mammalian) GLP-1 (24). The prolonged action was obtained by addition of a palmitic acid moiety to residue no 26 via a glutamic acid linker (also the the Lys in position 34 was changed to Arg to prevent acylation at this residue), inspired by the experience gained by the company with acylated insulin (detemir). The acylation results in albumin binding, prolongation of the absorption phase from the injection site, reduced degradation by the enzyme dipeptidyl peptidase 4 (DPP-4) and prevention of renal elimination. The modification resulted in a s.c. half-life of 12–13 hours. On the basis of the experience with liraglutide, semaglutide was developed from liraglutide by changing 3 things: (I) Ala in position 8 was substituted to Aib (alpha-amino-iso-butyric acid; a change known to result in complete DPP-4 resistance); (II) substitution of the palmitic acid with a C-20 di-acid; and (III) introduction of a longer and more flexible linker. This increased its half-life in humans to 165 hours without significantly changing its ability to activate the GLP-1 receptor (25,26). This was interpreted to support a once weekly scheme of administration. Importantly, semaglutide was developed not only with respect to long duration of action, but also on the basis of its ability to stimulate both insulin secretion and inhibit food intake, and was selected among hundreds of acylated GLP-1 analogues, varied with respect to the fatty acid moiety, the linker and the peptide backbone.

The safety and efficacy of semaglutide has been evaluated in a series of phase 2 and 3 clinical studies among which the first 6 trials have been presented in public. In a 12-week phase 2 study, semaglutide reduced HbA1c by impressive 1.7% from a baseline of 8.1% and lowered body weight by up to 4.8 kg, which was greater than with liraglutide 1.8 mg QD (27). Semaglutide doses of 0.5 and 1.0 mg and a 4-week dose escalation scheme were then selected for the SUSTAIN phase 3 program (27). In SUSTAIN-1, semaglutide 0.5 and 1.0 mg in patients with type 2 diabetes reduced HbA1c from a baseline of 8.1% by 1.4% and 1.5% compared with placebo after 30 weeks, and about 73% reached a HbA1c below 7.0% and 60% below 6.5% (28). Weight loss was 2.8 and 3.6 kg greater than with placebo, respectively (28). In the 56 weeks SUSTAIN 2 trial, semaglutide 0.5 and 1.0 mg reduced HbA1c by 1.3% and 1.6% versus 0.5% with sitagliptin (baseline: 8.1%). Weight losses were 4.3, 6.1 and 1.9 kg, respectively (29). In the SUSTAIN-3 trial, semaglutide was compared with exenatide QW. After 56 weeks, semaglutide 1.0 mg reduced HbA1c by 1.5% from a baseline HbA1c of 8.3%, compared with 0.9% with exenatide QW, and 67% *vs.* 40% reached a HbA1c <7.0%, respectively. Weight losses were 5.6 and 1.9 kg, respectively. Gastrointestinal adverse events occurred in 42% and 33%, and injection site reactions were

reported by 1.2% and 22% respectively. In SUSTAIN-4, semaglutide was compared with insulin glargine in insulin naïve patients. After 30 weeks, the reduction in HbA1c was 1.2%, 1.6% and 0.8% from a baseline of 8.2% with 0.5 and 1.0 mg of semaglutide and insulin glargine, respectively (30). Weight loss was 3.5 and 5.2 kg versus a weight gain of 1.2 kg with insulin glargine (30). Risk of hypoglycaemia was also reduced with semaglutide. Efficacy and safety of semaglutide versus placebo as add-on to basal insulin were investigated in SUSTAIN-5. After 30 weeks (baseline HbA1c 8.4%) 61% and 79% versus 11% with 0.5 mg, 1.0 mg or placebo had achieved a HbA1c below 7.0%. Weight losses were 3.7, 6.4 and 1.4 kg, respectively.

In SUSTAIN-6, semaglutide given once weekly was evaluated in two doses (0.5 or 1.0 mg) versus placebo in 3,297 patients with type 2 diabetic (21). At baseline 83% had established cardiovascular disease, chronic kidney disease or both. After 104 weeks, the primary outcome: cardiovascular death, nonfatal myocardial infarction or nonfatal stroke was reduced by 26%, P<0.001, nonfatal myocardial infarction by 26%, P=0.12 and nonfatal stroke by 39%, P=0.04) (21). Rates of all-cause-mortality as well as cardiovascular mortality were similar in the two groups. In total 45 patients would need to be treated for 2 years to prevent one primary endpoint. Revascularization surgery rates were also greatly reduced by semaglutide compared with placebo and rates of new or worsening of nephropathy were significantly lover, but rates of retinopathy complications significantly higher with semaglutide (21). A similar worsening of diabetic retinopathy was observed in the DCCT studies of intensified insulin therapy in patients with type 1 diabetes, and this side effect is currently not considered specifically associated with semaglutide therapy.

The SUSTAIN-7 trial is a head-to-head comparison between semaglutide and dulaglutide as add-on to metformin during 40 weeks (press release Novo Nordisk 17. August 2017). Patients in the 0.5 mg semaglutide group had a reduction in HbA1c of 1.5% against a 1.1% reduction in the 0.75 mg dulaglutide group. Additionally, 1.0 mg of semaglutide reduced HbA1c by 1.8% compared with a decrease by 1.4% among patients treated with 1.5 mg dulaglutide. Those on 0.5 mg semaglutide lost on average 4.6 kg of body weight compared to 2.3 kg with 0.75 mg dulaglutide. The higher doses led to losses of 6.5 kg and 3.0 kg, respectively. The side effects including changes in retinopathy did not differ between the two GLP-1 RAs.

Overall, semaglutide seems at least as effective and possible more potent than the other GLP-1RAs. The safety profile of semaglutide did not differ from those reported with other GLP-1 RAs (21,28). Semaglutide has not yet been approved for treatment of type 2 diabetes, but the advisory committee of the FDA in October 2017 unanimously recommended approval of semaglutide diabetes therapy.

The unusual efficacy of semaglutide, not the least with respect to loss of appetite, has inspired the company to develop semaglutide further for obesity without diabetes. It has been suggested that higher doses of GLP-RAs are needed for the weight loss effects, but the use of higher doses of semaglutide was not supported by the phase 2 studies. Because it was felt that the limiting side effects were mainly caused by plasma concentration peaks reached early after the weekly injections, it was decided to investigate lower, but daily doses. In this way, with an agent with a half-life of 165 hours, it should be possible to almost completely eliminate troughs and peaks. This was tested in a 52-week double-blind phase 2 clinical trial with once-daily subcutaneous semaglutide in 957 people with obesity, randomised to 0.05 to 0.4 mg/day or placebo (n=100 per group). In this trial, weight losses up to 17.8 kg from 111 kg (BMI, 39) (13.8% *vs.* 2.3% placebo) were observed (press release 2017).

The effectiveness of dulaglutide has also led to attempts to deliver this GLP-1 RA by the oral route (31). For this, semaglutide was co-formulated with SNAC {Sodium N-[8-(2-hydroxybenzoyl) Amino] Caprylate (Eligen^{R})}, developed by the company Emisphere. This allows a very rapid absorption from the gastrointestinal tract (within minutes). But because of the long half-life of the compound, daily dosing is appropriate. The bioavailability is rather low (a few per cent) and variable, but, again because of the long half-life of the compound, all that is needed is a small dose to "top up" what is already present. This means that the plasma levels remain relatively constant in spite of the variable absorption. OraI semaglutide was evaluated in a phase 2 study of 600 patients with T2DM and a baseline HbA1c of 7.9%; their weight was 92 kg. Semaglutide was dosed as 2.5–40 mg orally for 26 weeks, and the results were compared to those obtained with 1 mg subcutaneous semaglutide dosed weekly. HbA1c decreased from –0.7% to –1.9% as compared to –0.3% with placebo and –1.9% with semaglutide 1 mg s.c. once weekly. Those treated with placebo experienced a weight loos of –1 kg whereas the maximal weight loss with both oral and s.c. semaglutide was –6.5 kg; the side effects were said to be similar in those receiving the high doses of oral semaglutide and those receiving the subcutaneous injections, and were reported to

diminish over time (32).

The question remains why semaglutide seems more effective that the other GLP-1RAs, including liraglutide. This question cannot currently be answered; obviously, the high, rather constant levels of the compound may contribute and also its efficacy with respect to receptor activation, possibly resulting from the full DPP-4 protection and the improved linker function. The weight effect of the GLP-1RAs is believed to be exerted via receptors in the central nervous system. These receptors are probably reached by the agonists in their free, non-protein bound form via leaks in the blood brain barrier, particularly the area postrema, the subfornical organ and the median eminence (33). But it is also possible that the acyl moiety of the acylated compounds facilitate entry into additional regions of the CNS, and that liraglutide and semaglutide may differ in this respect.

The recent demonstration of positive cardiovascular effects of the GLP-1 RAs is extremely encouraging in relation to the clinical use of these compounds. The best results so far have been obtained with semaglutide in the SUSTAIN 6 trial as mentioned above (21). The MACE effect in this trial was driven by a reduction in the incidences of cardiovascular events (nonfatal stroke, nonfatal myocardial infarction), and there were also significant, large beneficial effects on kidney function and a marked, highly significant reduction in revascularization procedures. Strikingly, however, there were no effects on cardiovascular mortality. In addition, there were pronounced effects on HbA1c and body weight. This might suggest that the therapy prevented these events from happening, and that the preventive effect was possibly due to the metabolic effects of the compound. Further studies are, however, required to settle this question, but the beneficial effect of the drug remains even though an explanation is currently unavailable.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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