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REVIEW ARTICLE

Pharmacokinetics and Clinical Implications of Semaglutide: A New Glucagon-Like Peptide (GLP)-1 Receptor Agonist

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Abstract Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) came to market in the year 2005, as a new therapeutic classification, for clinical use in the management of type 2 diabetes mellitus (T2DM). Since 2005, there have been six approved products on the market, with the newest product being semaglutide (Novo Nordisk). Several studies have been conducted and completed evaluating its pharmacokinetics as a once-weekly subcutaneous injection. As a dose of 0.5 or 1 mg, semaglutide has a half-life of 7 days; therefore, it would reach steady state in 4–5 weeks. There are few drug interactions and dose adjustments are not necessary. However, similar to other GLP-1 RAs, semaglutide can delay gastric emptying and may impact the absorption of oral medications. Based on clinical trials, semaglutide has been compared with placebo, sitagliptin, exenatide extended release, and insulin glargine as monotherapy or add-on therapy. Semaglutide has resulted in a 1.5–1.9% glycosylated hemoglobin A_{1c} reduction after 30–56 weeks. It also produced 5–10% weight reduction from baseline in clinical efficacy studies. Semaglutide can be another acceptable option for patients with T2DM, and it has a potential role among patients who require weight loss with a low risk of hypoglycemia. This article evaluates the pharmacokinetics of semaglutide and summarizes its application to clinical practice based on efficacy and safety data.

Key Points

Semaglutide is a new glucagon like peptide-1 receptor agonist for the management of type 2 diabetes.

Semaglutide is an effective option due to improved glycemic control, weight loss, and low risk of hypoglycemia.

Additional studies will determine its efficacy and safety in patients with obesity.

1 Introduction

In the USA, there are an estimated 30.3 million people diagnosed with diabetes mellitus; the incidence of new diagnoses is 1.5 million people per year [1]. Comparatively, there are approximately 422 million individuals affected with diabetes worldwide [2]. Due to the growing evidence regarding the pathophysiology of type 2 diabetes (T2DM), it is essential to individualize therapy for a patient based on several factors (i.e., patient preference, degree of glycosylated hemoglobin A_{1c} (HbA_{1c}) lowering, risk of hypoglycemia, cost, effect on weight).

In the guidelines from the American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE), metformin is recommended as first-line therapy for the management of T2DM. Metformin has been a mainstay medication as monotherapy and/or in

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combination with other anti-hyperglycemic agents, as long as the patient does not have a contraindication to metformin [3, 4]. Glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1 RAs) are recommended as a second-line medication in both published guidelines, with liraglutide being the preferred GLP-1 RA, according to the ADA, due to its cardiovascular evidence [3–5]. While the AACE guidelines follow a hierarchy with recommendations, GLP-1 RAs are options for patients requiring glycemic control, satiety control, and weight loss due to their mechanism of action—promoting insulin secretion from β cells while decreasing glucagon secretion in the α cells of the pancreas, promoting satiety in the brain, and slowing gastric emptying in the intestines [3, 4].

Since 2005, there have been six GLP-1 RAs approved by the US Food and Drug Administration (FDA). Table 1 summarizes the clinical characteristics of these six medications. Semaglutide is the seventh GLP-1 RA approved in the USA on 5 December 2017 (Ozempic®, Novo Nordisk) and may be the second GLP-1 RA also indicated for obesity management. Albiglutide (marketed as Tanzeum®, GlaxoSmithKline) will be discontinued from the US market in July 2018. This article reviews the pharmacokinetics, pharmacodynamics, clinical evidence, safety, dosage, and administration of semaglutide to predict its clinical implications for practice. The purpose of this review is to summarize and highlight evidence regarding semaglutide for the management of T2DM, as a newly approved GLP-1 RA, but also as a future option for the management of obesity.

2 Chemistry and Pharmacology

GLP-1 is a gastrointestinal hormone and rapidly degraded by dipeptidyl peptidase-4 (DPP-4) enzyme, resulting in a short half-life. GLP-1 RAs have been developed to be similar in structure to endogenous GLP-1, but have different structural components in order to provide the beneficial effects of GLP-1. Semaglutide is a human GLP-1 analog, studied for the management of T2DM and obesity. It has a structure with 94% homology with human GLP-1. However, it has specific modifications at position 8, 26, and 34 to extend its half-life, allowing for once-weekly administration [6].

As a GLP-1 RA, semaglutide has four different mechanisms of action to control blood glucose levels and promote weight loss. To improve glycemic control, semaglutide promotes insulin secretion from β cells and suppresses glucagon secretion from α cells in the pancreas. To promote weight loss, semaglutide slows gastric emptying; in addition, semaglutide promotes satiety due to its low molecular weight [6].

2.1 Pharmacokinetics

The long half-life and low rate of total plasma clearance of semaglutide support once-weekly administration.

2.2 Absorption

Table 2 provides pharmacokinetic results from semaglutide studies. In healthy adults, subcutaneous administration of one-time semaglutide 0.5 mg reached maximum concentration (C_{max}) in 24–56 h [7, 8]. Dose-escalation studies using weekly semaglutide 0.25 mg doses for four doses, followed by 0.5 mg doses for four doses and then 1.0 mg for five doses showed similar time to C_{max} (t_{max}) of 33–36 h after the final 1.0 mg dose [9, 10]. C_{max} and area under the plasma concentration–time curve (AUC) are similar following a single 0.5 mg dose and, likewise, are also similar following the final 1.0 mg dose of a dose-escalation strategy [7–10]. Subcutaneous bioavailability of semaglutide is approximately 94%, the highest of all currently available GLP-1 RAs (Table 3) [11–14].

2.3 Distribution

Semaglutide was developed with the intent to design a liraglutide analog with increased affinity for albumin binding to provide once-weekly dosing of a GLP-1 RA. In

Table 1 Characteristics of glucagon-like peptide-1 receptor agonists

Brand name	Generic name	FDA approval	Homology (%)	Half-life	Frequency/administration
Adlyxin™ [32]	Lixisenatide	August 2016	50	3 h	Once daily/SC
Bydureon® [33]	Exenatide ER	March 2014	53	2 weeks	Once weekly/SC
Byetta® [34]	Exenatide IR	April 2005	53	2.4 h	Twice daily/SC
Ozempic® [35]	Semaglutide	December 2017	94	1 week	Once weekly/SC
Tanzeum® [36]	Albiglutide	April 2014	97	5 days	Once weekly/SC
Trulicity® [13]	Dulaglutide	September 2014	90	5 days	Once weekly/SC
Victoza® [12]	Liraglutide	January 2010	97	13 h	Once daily/SC

ER extended-release, *FDA* US Food and Drug Administration, *IR* immediate-release, *SC* subcutaneously

Table 2 Summary of findings from healthy individuals in pharmacokinetic trials [7–10]

Study	Semaglutide dosing prior to study measurements	t_{max} (h)	C_{max} (nmol/L)	AUC (nmol h/L)	$t_{½}$ (h)
Marbury et al. [7]	Single 0.5 mg dose	24	10.3	2600	183
Jensen et al. [8]	Single 0.5 mg dose	56	10.9	3123	168
Blundell et al. [9] [a]	Weekly 0.25 mg dose (4 weeks), weekly 0.5 mg dose (4 weeks), weekly 1.0 mg dose (5 weeks)	33	32	4467	N/A
Kapitza et al. [10][a]	Weekly 0.25 mg dose (4 weeks), weekly 0.5 mg dose (4 weeks), weekly 1.0 mg dose (5 weeks)	36	33.8	4602	165

AUC area under the plasma concentration–time curve, C_{max} maximum (or peak) serum concentration, *N/A* not applicable, $t_{½}$ half-life, t_{max} time to maximum serum concentration

[a]Values represent steady state of final 1.0 mg dose after 12 weeks of treatment

Table 3 Subcutaneous bioavailability of available glucagon-like peptide-1 agonists [11–14]

GLP-1 agonist	Subcutaneous bioavailability (%)
Semaglutide	94
Liraglutide	55–66
Dulaglutide	47–65
Exenatide	62
Lixisenatide	Unknown[a]

GLP-1 glucagon-like peptide-1

[a]The sponsor of lixisenatide did not perform absolute bioavailability studies

the foundation study that led to the creation of semaglutide, Lau et al. [11] showed that in in vivo characterization studies in pigs, the half-life of semaglutide after intravenous administration was 46.1 h compared with the 12.4-h half-life of liraglutide [11]. Semaglutide showed a higher volume of distribution (0.102 L/kg) than liraglutide (0.067 L/kg) and slower body clearance (0.0016 vs. 0.0038 L/h/kg), indicating higher albumin binding and time spent in the body. Subcutaneous mean residence time following subcutaneous administration of semaglutide was 63.6 h compared with 23.0 h for liraglutide [11]. There were no toxic effects noted in this study resulting from the higher mean residence time of semaglutide than of liraglutide. In the clinical trials discussed here, semaglutide caused more gastrointestinal adverse effects than exenatide, possibly due to longer mean residence time, but had a similar adverse effect profile to liraglutide [15, 16] (see Table 4).

2.4 Metabolism

The metabolism of semaglutide was studied in an absorption, metabolism, and excretion study in seven male participants who received a single subcutaneous dose of radiolabeled [^{3}H]-semaglutide [8]. Metabolite profiling indicated that semaglutide was metabolized to six different metabolites identified as P1–P3 and P5–P7. P4 represents the parent compound [^{3}H]-semaglutide, which was the primary component detected in plasma (82.6%). Semaglutide is metabolized by proteolytic cleavage of the peptide backbone and β-oxidation of the fatty acid side chain. Concentration of metabolites declined over time, with only the parent compound detected in plasma at 28 days post-dose. It is unknown what role the metabolites have in efficacy or adverse effects.

2.5 Elimination

In the study mentioned in Sect. 2.4, excretion of radiolabeled [^{3}H]-semaglutide and its metabolites was also described [8]. Following 64 days of collection after a one-time subcutaneous dose of semaglutide 0.5 mg, 75.1% of the dose was recovered, with 53% in urine, 18.6% in feces, and 3.2% in expired air. Parent semaglutide and 21 metabolites were detected in urine, and 3.1% of the administered dose was found to be [^{3}H]-semaglutide, with two metabolites (P6 and P7) each accounting for 14% of the administered dose, and all other metabolites accounting for $\leq$ 1.8% of the administered dose. The minimal amount of intact drug in the urine indicates that renal dosing may not be needed for semaglutide. No parent drug was detected in feces.

3 Special Populations

3.1 Renal Impairment

The effect of renal impairment (RI) on semaglutide pharmacokinetics and tolerability was studied in 56 patients with varying degrees of renal function categorized as having normal renal function, mild RI, moderate RI, severe RI, and end-stage renal disease (ESRD) requiring

Table 4 Summary of glycosylated hemoglobin-lowering ability of semaglutide from SUSTAIN trials [15, 16, 19–22]

	Mean reduction in HbA_{1c}				Percentage achieving $HbA_{1c} < 7\%$				Percentage achieving $HbA_{1c} \leq 6.5\%$			
	Semaglutide		Comparator		Semaglutide		Comparator		Semaglutide		Comparator	
	0.5 mg	1 mg			0.5 mg	1 mg			0.5 mg	1 mg		
SUSTAIN 1 Semaglutide vs. placebo	− 1.45	− 1.55	− 0.02		74	72	25		59	60	13	
SUSTAIN 2 Semaglutide vs. sitagliptin 100 mg as an add-on to metformin, TZDs, or both	− 1.3	− 1.6	− 0.5		69	53	36		53	66	20	
SUSTAIN 3 Semaglutide vs. exenatide ER 2 mg as add-on to 1 or 2 oral agents	N/A	− 1.5	− 0.9		N/A	67	40		N/A	47	22	
SUSTAIN 4 Semaglutide vs. insulin glargine as add-on to metformin ± sulfonylureas	− 1.21	− 1.64	− 0.83		57	73	38		37	54	18	
SUSTAIN 5 Semaglutide vs. placebo as add-on to basal insulin ± metformin	− 1.4	–1.8	− 0.1		61	79	11		41	61	5	
SUSTAIN 7	**Low dose**	**High dose**	**Low dose**	**High dose**	**Low dose**	**High dose**	**Low dose**	**High dose**	**Low dose**	**High dose**	**Low dose**	**High dose**
Semaglutide low (0.5 mg) and high dose (1.0 mg) vs. dulaglutide low (0.75 mg) and high dose (1.5 mg) as add-on to metformin	− 1.5	− 1.8	− 1.1	− 1.4	68	79	52	67	49	67	34	47

ER extended release, *HbA_{1c}* glycosylated hemoglobin, *N/A* not applicable, *TZDs* thiazolidinediones

hemodialysis who received one time subcutaneous semaglutide 0.5 mg doses [7]. C_{max} was 10–20% higher in subjects with RI than in those with normal renal function; however, there was no trend in severity of RI and C_{max}. In an analysis of covariance model adjusted for age, sex, and body weight, there were no differences in AUC among the different groups. Comparisons of point estimates of AUC pre- and post-dialysis in subjects with ESRD showed no significant differences, indicating the hemodialysis has little impact on semaglutide. There was also no difference in protein binding across the groups.

RI is a common complication of diabetes, making it essential to understand renal dosing of anti-hyperglycemic agents. The study discussed in this section [7] provides evidence that the pharmacokinetics of semaglutide are not affected by RI, and thus renal dose adjustments may not be necessary. Patients with all stages of RI were included in the landmark SUSTAIN trials, which showed similar safety and efficacy compared with patients with normal renal function.

3.2 Hepatic Impairment

A phase I single-dose pharmacokinetic trial showed no need for dose adjustment in patients with varying levels of hepatic function [17]. Further, the effect of hepatic impairment on semaglutide pharmacokinetics was studied in 44 patients with normal hepatic function or mild, moderate, or severe hepatic impairment for 5 weeks following a single 0.5 mg subcutaneous dose [18]. There was no significant difference in AUC or C_{max} among the four groups, indicating that hepatic impairment does not affect semaglutide exposure. The t_{max} and the half-life of the drug were also similar across all groups. Despite reduced concentrations of albumin in hepatic impairment, plasma protein binding of semaglutide was > 99% in all groups, so a large amount of unbound drug should not be expected in patients with liver dysfunction. Additionally, the SUSTAIN trials included patients with hepatic impairment and found no differences in the safety profile [15, 16, 19–23].

4 Drug Interactions

Semaglutide coadministered with metformin, warfarin, digoxin, atorvastatin, ethinyl estradiol, and levonorgestrel has been studied to determine potential drug–drug interactions. As semaglutide lacks a specific route for metabolism, there is no drug–drug interaction between semaglutide and these medications; therefore, dose adjustments are not necessary [24, 25]. However, caution is warranted regarding the absorption of oral medications, as semaglutide delays gastric emptying [26].

5 Evidence of Efficacy in Type 2 Diabetes Mellitus

The efficacy of semaglutide was studied in the SUSTAIN trials [1–5, 7] and a series of phase IIIa randomized trials.

SUSTAIN 1 compared weekly semaglutide 0.5 or 1 mg monotherapy with placebo among treatment-naïve adults with T2DM insufficiently controlled by lifestyle management alone [19]. The study enrolled 387 participants in study sites located in eight countries, including the USA. Baseline characteristics were generally similar among the treatment and control arms. The primary outcome was change in mean HbA_{1c} from baseline to 30 weeks. Both the 0.5 and 1 mg doses of semaglutide produced significantly larger reductions in HbA_{1c} than placebo: -1.45% (95% confidence interval [CI] -1.65 to -1.26; $P < 0.0001$) and -1.55% (95% CI -1.74 to -1.36; $P < 0.0001$), respectively. This reduction in HbA_{1c} is greater than seen in other GLP-1 RA clinical trials compared with placebo (Fig. 1) [27]. Further analysis showed that 74% of participants in the semaglutide 0.5 mg arm (odds ratio [OR] 16.92, 95% CI 8.44–33.89) and 72% of participants in the 1 mg arm (OR 15.70, 95% CI 8.00–30.83) achieved a goal HbA_{1c} of $< 7\%$ compared with 25% of participants in the placebo arm. When using the more intense HbA_{1c} goal of $\leq 6.5\%$, semaglutide 0.5 and 1 mg achieved target HbA_{1c} in 59% of participants (OR 15.99, 95% CI 7.82–32.68) and 60% of participants (OR 18.34, 95% CI 8.96–37.54) compared with 13% of placebo recipients. Semaglutide doses in SUSTAIN 1 also showed a significant reduction in mean body weight compared with placebo, the secondary endpoint of the study. While not significant, there were trends towards lower systolic and diastolic blood pressure similar to effects seen in other studies [19].

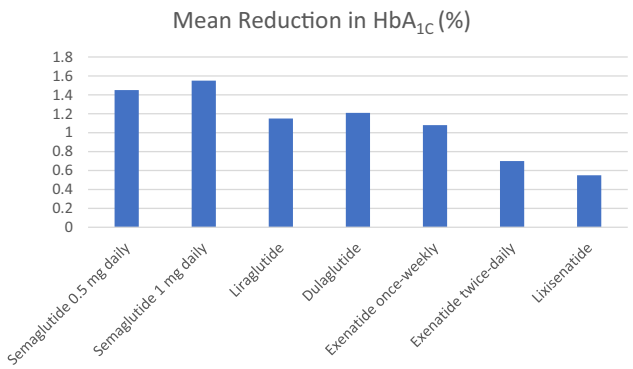

Fig. 1 Mean reduction in glycosylated hemoglobin (HbA_{1c}) of glucagon-like peptide-1 analogs compared with placebo [27]

In SUSTAIN 2, investigators compared semaglutide 0.5 and 1 mg weekly with 100 mg daily of the DPP-4 inhibitor sitagliptin [20]. Eligible patients were adults with T2DM inadequately controlled on metformin, thiazolidinediones, or both. Study sites were in 18 countries (not the USA) with a total of 1231 enrolled participants. Baseline characteristics were similar among the three groups, except HbA_{1c} was slightly higher in the sitagliptin arm (8.2%) than in each semaglutide arm (8.0% in both). The primary outcome, mean HbA_{1c} change from baseline to 56 weeks, showed significantly greater reduction in both semaglutide arms compared with sitagliptin. Semaglutide 0.5 mg produced a –1.3% mean reduction in HbA_{1c} (95% CI -1.42 to -1.21; $P < 0.0001$) and semaglutide 1 mg produced a –1.6% mean reduction in HbA_{1c} (95% CI -1.71 to -1.51; $P < 0.0001$) compared with -0.5% in patients randomized to sitagliptin. Similar to SUSTAIN 1, the secondary outcomes were the proportion of participants achieving a reduction in HbA_{1c} goals of < 7 and $\leq 6.5\%$. These goals were achieved by 69 and 53% of participants in the semaglutide 0.5 mg arm and 78 and 66% in the semaglutide 1 mg arm compared with 36 and 20% of participants in the sitagliptin arm. Both doses of semaglutide resulted in significantly higher proportions of participants achieving these goals compared with sitagliptin ($P < 0.0001$). Additionally, both doses of semaglutide significantly reduced body weight and systolic blood pressure compared with sitagliptin [20].

SUSTAIN 3 compared semaglutide 1 mg with weekly exenatide extended release (ER) 2 mg in adults with T2DM not controlled on one or two oral antidiabetic agents [15]. The study enrolled 819 subjects in 12 countries, including the USA. The two study groups did not differ in baseline characteristics, and 96.5, 48.1, and 2.3% of patients were on biguanides, sulfonylureas, and thiazolidinediones, respectively. In terms of primary outcome, at 56 weeks, semaglutide resulted in a significantly larger reduction in HbA_{1c} of 1.5%, compared with 0.9% by exenatide ($P < 0.0001$). Achievement of target HbA_{1c} was significantly higher among subjects taking semaglutide, with 67% reaching $HbA_{1c} < 7.0$ and 47% reaching $HbA_{1c} \leq 6.5\%$, while in the exenatide group 40 and 22% achieved these goals, respectively ($P < 0.0001$ for both HbA_{1c} targets). Semaglutide also showed significantly greater reductions of body weight, body mass index (BMI),

weight circumference, and systolic blood pressure than exenatide ($P < 0.05$) for all measures [15].

SUSTAIN 4 compared semaglutide 0.5 or 1 mg with insulin glargine as add-on therapy for insulin-naïve patients with T2DM not adequately controlled on metformin monotherapy or in combination with a sulfonylurea [21]. Participants randomized to receive insulin were initiated on 10 units daily; a titration protocol was followed to achieve target pre-breakfast plasma glucose levels of 72–99 mg/dL. The mean insulin dose at the end of the study was 29.2 units. This trial enrolled 1089 patients in 14 countries, including the USA. There were no significant baseline differences between treatment groups. Of the study population, 48% received metformin monotherapy and 52% metformin plus a sulfonylurea. Primary and secondary outcomes were the same as the previous SUSTAIN trials. At 30 weeks, the mean HbA_{1c} reduction in the semaglutide 0.5 mg group was -1.21 (95% CI -1.31 to -1.10; $P < 0.0001$) and in the semaglutide 1 mg group was -1.64 (95% CI -1.74 to -1.54; $P < 0.0001$) compared with -0.83% in the insulin glargine group. Target HbA_{1c} levels $< 7.0\%$ (OR 2.39, 95% CI 1.73–3.28) were achieved by 57% of participants in the semaglutide 0.5 mg group and 73% of the semaglutide 1 mg group (OR 5.78, 95% CI 4.08–8.19) versus 38% of participants receiving insulin glargine. Similarly, semaglutide 0.5 and 1 mg resulted in greater proportions of patients achieving lower HbA_{1C} levels $\leq 6.5\%$: 37% (OR 3.02, 95% CI 2.11–4.33) and 54% (OR 6.86, 95% CI 4.76–9.89), respectively, compared with 18% of participants in the insulin glargine group. Similar to the prior SUSTAIN trials, secondary endpoints demonstrated greater reduction in mean body weight and systolic blood pressure than insulin glargine [21].

SUSTAIN 5 has not been fully published at the time of writing, but results were presented as a poster at the European Association for the Study for Diabetes in 2016 [22]. It was a double-blinded, placebo-controlled, parallel-group, multicenter trial that compared semaglutide 0.5 and 1.0 mg with placebo in 397 patients with T2DM on stable treatment with basal insulin alone or in combination with metformin. The primary endpoint was change in HbA_{1c} after 30 weeks. Baseline characteristics were similar between groups and included an average age of 58 years, HbA_{1c} of 8.4%, and BMI of 32 kg/m^2. The mean HbA_{1c} reduction at week 30 was 1.4% and 1.8% with semaglutide 0.5 and 1.0 mg, respectively, and 0.1% with placebo ($P < 0.0001$ for both). Insulin doses also decreased by 10, 15, and 4% when comparing semaglutide 0.5 mg, 1.0 mg, and placebo, respectively ($P = 0.0046$ and $P < 0.0001$ compared with placebo) [22].

SUSTAIN 7 was a randomized, open-label, active-controlled trial in 1201 patients over 40 weeks [16]. Patients were randomized to semaglutide 0.5 mg, dulaglutide 0.75 mg, semaglutide 1.0 mg, or dulaglutide 1.5 mg weekly. The primary endpoint was change in HbA_{1c} from baseline at week 40. Baseline characteristics were similar between groups and included mean HbA_{1c} of 8.2%, age 55–56 years, and mean BMI of 33 kg/m^2. In total, 301 patients were randomized to semaglutide 0.5 mg, 299 to dulaglutide 0.75 mg, 300 to semaglutide 1.0 mg, and 299 to dulaglutide 1.5 mg weekly. The mean percentage HbA_{1c} was reduced by 1.5% with semaglutide 0.5 mg and 1.1% with dulaglutide 0.75 mg ($P < 0.0001$). Mean HbA_{1c} was reduced by 1.8% with semaglutide 1.0 mg versus 1.4% with dulaglutide 1.5 mg ($P < 0.00001$). The authors concluded that at low and high doses, semaglutide was superior to dulaglutide for lowering HbA_{1c} [16].

6 Oral Semaglutide

The SUSTAIN trials demonstrated positive effects of subcutaneous semaglutide on glycemic control; however, injections can be a barrier to medication adherence. For this reason, an oral tablet containing semaglutide formulated with an absorption enhancer is in clinical development. A phase II trial compared various doses (2.5, 5, 10, 20, 40 mg) and dosing regimens (daily 2.5 mg, standard dose escalation, and rapid dose escalation) of oral semaglutide with once-weekly subcutaneous semaglutide 1 mg and oral placebo [28]. All doses and formulations of semaglutide showed a significantly greater mean reduction in HbA_{1c} than oral placebo at 26 weeks. Mean reduction in HbA_{1c} increased as oral semaglutide doses increased, with semaglutide 40 mg having comparable HbA_{1c} reductions with the subcutaneous formulation, both resulting in 1.9 reductions. In addition to HbA_{1c} reduction, secondary outcome analysis revealed that oral doses of semaglutide 10 mg and higher resulted in a significantly greater reduction in body weight than placebo. It is not known what the bioavailability of oral semaglutide is, but based on these results in which 40 mg of oral drug produced effects similar to 1 mg subcutaneously, it is presumably much less than 100%.

7 Obesity

The weight loss effects of semaglutide have been studied among small patient populations, as preliminary evidence [26, 29, 30]. In a double-blinded, crossover study, semaglutide was evaluated among 30 patients with obesity [29]. Semaglutide 1 mg weekly was compared with placebo to determine the effect on energy intake and appetite control. Overall, semaglutide reduced measures of appetite on a visual analog scale ($P = 0.0023$) in comparison with

placebo. Nausea was the most common adverse event, but was similar between the two groups. Patients receiving semaglutide had less hunger and fewer food cravings; due to reduced intake and improved control of eating, semaglutide resulted in a 5.0 kg weight loss from baseline (101.3 kg), compared with a weight increase with placebo (1.0 kg). In another study, semaglutide 1 mg weekly was compared with placebo among 30 patients with obesity [26]. Due to semaglutide and its mechanism of action, improvements in metabolic marks, such as fasting insulin, C-peptide, and lipoprotein concentrations, are observed. While there was no difference between semaglutide and placebo in post-prandial gastric emptying, semaglutide did reduce gastric emptying within the first hour after a standardized high-fat breakfast. This preliminary evidence indicates the potential use of semaglutide in patients with obesity with and without diabetes.

In a phase II study, approximately 1000 patients were randomized to various doses of semaglutide; this study was double-blinded and lasted for 52 weeks in order to determine the dose–response of semaglutide for weight loss [30]. There were approximately nine groups with roughly 100 patients, and the dose of semaglutide varied from 0.05 to 0.4 mg/day. One of the nine groups was the placebo comparator. All patients received counseling on lifestyle modifications with caloric reduction and physical activity. Baseline weight was 111 kg with a BMI of 39 kg/m^2. After 52 weeks of treatment, semaglutide produced a 17.8 kg weight loss (approximately 16% from baseline), whereas the placebo arm only produced a 2.3% weight loss [27]. As the results have not been fully released, it is not known what the proportion of patients with and without diabetes in the trial was. Semaglutide will be investigated among patients who are overweight and those with obesity, in phase III trials starting in 2018; it will be several years until the final datasets are reported and published.

Currently, there is evidence of weight loss among patients with T2DM who have obesity from the SUSTAIN trials. As mentioned earlier, there were significant differences in weight loss with semaglutide and the comparator ($P < 0.0001$) in the SUSTAIN 2, 3, and 4 trials [15, 20, 21]. Specifically, from these three trials, semaglutide 0.5 mg produced a 3.47 kg (SUSTAIN 4) and 4.6 kg (SUSTAIN 2) weight loss in comparison with –6.1 kg (SUSTAIN 2) and –5.17 kg (SUSTAIN 4) with semaglutide 1 mg [20, 21]. It is important to note that the sitagliptin group lost weight (1.9 kg) during the SUSTAIN 2 trial, whereas patients in the insulin glargine group gained weight (1.15 kg; SUSTAIN 4) [20, 21]. In the SUSTAIN 3 trial, semaglutide was compared with another once-weekly GLP-1 RA (exenatide) and had greater reductions in weight of 5.6 kg compared with –1.9 kg with exenatide [15]. In the SUSTAIN 5 trial, patients receiving semaglutide 0.5 and 1.0 mg had a 3.7 and 6.4 kg weight loss, respectively, compared with − 1.4 kg with placebo [22]. These effects were observed over 30 weeks. In addition, semaglutide had greater weight loss effects than dulaglutide over 40 weeks, as reported in the SUSTAIN 7 trial [16]. Those receiving semaglutide 0.5 mg had an average weight loss of 4.6 kg compared with − 2.3 kg with dulaglutide 0.75 mg ($P < 0.0001$). With a higher dose, semaglutide 1 mg produced a 6.5 kg weight loss, compared with − 3.0 kg with dulaglutide 1.5 mg ($P < 0.0001$) [16].

8 Cardiovascular Disease

The SUSTAIN 6 trial was completed in accordance with FDA regulations requiring that all new medications for T2DM not be associated with increased cardiovascular risk [23]. This randomized, double-blind, placebo-controlled trial enrolled 3297 patients with T2DM aged 50 years and older to receive semaglutide (dose escalation to 0.5 or 1 mg subcutaneously weekly) or placebo (0.5 or 1 mg subcutaneously weekly). Background therapy was provided in the form of current best practices for glycemic control (treatment with a DPP-4 was an exclusion criteria), blood pressure control, and lipid control. Drug therapy and other patient characteristics were evenly distributed at baseline. The primary outcome was a composite of major adverse cardiac event (MACE) comprised of death from cardiovascular causes, non-fatal myocardial infarction, and non-fatal stroke. Semaglutide was associated with lower rates of the primary outcome (6.6% vs. 8.9% [hazard ratio {HR} 0.74, 95% CI 0.58–0.95; $P < 0.001$ for non-inferiority, $P = 0.02$ for superiority) than placebo. Of the composite endpoint, non-fatal stroke was most significantly reduced, occurring in 1.6% of patients in the semaglutide arm versus 2.7% in the placebo arm (HR 0.61, 95% CI 0.38–0.99; $P = 0.04$). Cardiovascular death was similar between the two arms (2.7 vs. 2.8%; $P = 0.92$). The secondary outcome, an expanded composite outcome including death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, coronary or peripheral revascularization, and hospitalization for unstable angina or heart failure was also reduced, occurring in 12.1% of participants in the semaglutide arm and 16.0% of participants receiving placebo (HR 0.74, 95% CI 0.62–0.89; $P = 0.002$). This result was driven by reduced revascularization among participants in the semaglutide arm (5.0 vs. 7.6%) [HR 0.65, 95% CI 0.50–0.86; $P = 0.003$]. In addition to primary and secondary outcomes, semaglutide showed statistically significant lowering of systolic blood pressure by an average of − 2.59 mmHg ($P < 0.001$) and lipids by an average of − 0.92 mg/dL ($P < 0.001$). While these values may not be clinically significant, they may contribute to the

cardiovascular benefits of semaglutide shown in this trial and are consistent with findings in the previous SUSTAIN trials.

9 Safety and Tolerability

The adverse events of semaglutide are similar to other GLP-1 RAs, with gastrointestinal adverse events occurring most frequently. In clinical trials, nausea peaked after treatment initiation and diminished over time; it is observed with both the oral and subcutaneous formulations. Slow dose titration reduces the incidence of gastrointestinal adverse effects [19–21, 23]. All GLP-1 RAs are contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) and in patients with multiple endocrine neoplasia syndrome type 2 (MEN 2) because of dose- and treatment duration-dependent thyroid C cell tumors discovered in rats and mice. This finding has not been observed in humans related to any GLP-1 RA use.

In the SUSTAIN 1 trial, nausea was reported in 26 (20%) patients randomized to semaglutide 0.5 mg, 31 (24%) patients who received semaglutide 1.0 mg, and ten (8%) patients who received placebo, and diarrhea was reported in 16 (13%) patients who received semaglutide 0.5 mg, 14 (11%) patients who received semaglutide 1.0 mg, and three (2%) patients who received placebo. There were no cases of pancreatitis and four cases of cholelithiasis in the semaglutide groups compared with none in the placebo group [19]. SUSTAIN 6 had a similar incidence of gallbladder disorder between groups (58 patients in semaglutide vs. 61 in placebo), although slightly more cases of cholelithiasis (4.6 vs. 3.8%) [23]. More malignant neoplasms were reported in the semaglutide groups (four in total) than in the placebo group (none) in SUSTAIN 1, while the much larger SUSTAIN 6 trial had an equal distribution of malignant neoplasms. Similar rates of hypoglycemia were observed as compared with placebo.

There were lipase and amylase increases observed with use of semaglutide, although no increases in the incidence of pancreatitis. Initial case reports of acute pancreatitis with exenatide, the first GLP-1 RA to come to market, have been published so it is recommended that patients be monitored for signs of pancreatitis with all other GLP-1 RAs and discontinue use if suspected. A minor increase in pulse rate and decrease in systolic blood pressure was observed in clinical trials, comparable to findings with other GLP-1 RAs [19–21, 23]. For example, in the SUSTAIN 6 trial the mean pulse rate in the semaglutide group was 2.0 beats per min (bpm) higher in the 0.5 mg group and 2.5 bpm higher in the 1.0 mg group than with placebo ($P < 0.001$ for both comparisons) [23]. It is not known if there is any clinical significance to the increased pulse rate, especially in light of the overall demonstrated cardiovascular benefits.

In the SUSTAIN 6 trial, rates of retinopathy complications, including vitreous hemorrhage, blindness, or conditions requiring treatment with an intravitreal agent or photocoagulation, were significantly higher in the semaglutide group (3.0%, $n = 50$) than with placebo (1.8%, $n = 29$) (HR 1.76, 95% CI 1.11–2.78; $P = 0.02$). Most had pre-existing retinopathy at baseline (84% in semaglutide group and 82.85% in placebo group). This is a unique finding that was not seen with other GLP-1 RAs and the cause is not known; however, it is thought that large, rapid improvements in HbA_{1c} may cause transient worsening of diabetic retinopathy [23, 31].

10 Clinical Implications

As summarized, semaglutide is a new long-acting GLP-1 RA with once-weekly administration made possible by its pharmacokinetic profile. Additional head-to-head studies should be conducted; more evidence will become available as subcutaneous semaglutide 0.5 and 1 mg per week is being compared with dulaglutide 0.75 and 1.5 weekly by subcutaneous injection in SUSTAIN 7. In this trial, semaglutide has demonstrated superior efficacy with a 1.8% HbA_{1c} reduction at 1 mg per week when compared with both doses of dulaglutide [16]. This finding was statistically significant, even though the results have not yet been published. In addition, this dose of semaglutide also produced a 6.5 kg weight loss from baseline, after 40 weeks of therapy. Additional trials are underway to assess the role of semaglutide among patients with obesity, with or without T2DM.

The change in HbA_{1c} levels was the primary outcome of the SUSTAIN 1, 2, 3, and 4 trials [15, 19–21]. In addition, there were other endpoints, such as the rate of hypoglycemia, nausea, and change in body weight. Based on the SUSTAIN trials, semaglutide is a superior option when used as monotherapy or as add-on therapy to oral antihyperglycemic agents or insulin. There is a predicted 1.6% HbA_{1c} reduction and estimated 4.5 kg weight loss with semaglutide over 6–12 months in patients with T2DM. While the efficacy and safety of semaglutide are positive, long-term evidence is needed to determine the clinical effect on glycemic control beyond 52 weeks. In addition, the role of semaglutide is not known among individuals with HbA_{1c} levels above 10% or with known proliferative retinopathy or maculopathy; these individuals were excluded from the SUSTAIN trials [15, 16, 19–23].

As a disposable, pre-filled pen, semaglutide can be injected in the subcutaneous portion of the abdomen, thigh, or upper arm for once-weekly administration [25]. Similar

to the SUSTAIN trials, a patient can be initiated on a 0.25 mg dose for 4 weeks. After 4 weeks, the dose can be increased to 0.5 mg and then 1 mg after an additional 4 weeks. If a single dose is missed, the patient should be instructed and counseled to administer the medication within 5 days of the missed dose. Semaglutide will only be available in a pre-filled device in cartons of one to two pens. If dispensed as a carton of one pen, the carton should be used as initial treatment of 0.25 mg to a maintenance dose of 0.5 mg. If dispensed as a carton of two pens, the carton should be used as the maintenance dose of 1 mg per week. The pen can be stored in the refrigerator until use; after the first use, the pen can be stored in the refrigerator or at room temperature for 56 days [25]. The cost or insurance coverage of semaglutide is unknown as the medication will not be available until early 2018.

11 Conclusion

Semaglutide produced greater HbA_{1c} reductions than active groups (i.e., sitagliptin, exenatide ER, and insulin glargine) in patients with T2DM and thus far has shown consistent weight loss among patients with and without diabetes. In clinical practice, there may be several advantages to semaglutide, such as weight loss and low risk of hypoglycemia. Semaglutide has a predictable pharmacokinetic profile, allowing for a longer duration of action and once-weekly subcutaneous administration. There are limited drug interactions and no dosing adjustments in patients with renal or liver impairment. Therefore, semaglutide is an option, most likely as add-on therapy, for improved glycemic control, weight loss, and reduced risk of hypoglycemia. Similarly, to other GLP-1 RAs, the most common adverse event associated with semaglutide is nausea. It may have more advantages for clinical use once additional data are published regarding the oral formulation and potential indication for obesity management. Overall, semaglutide is an option, with diet and exercise, for the management of T2DM.

Compliance with Ethical Standards

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