SUSTAINable management of type 2 diabetes: feasibility of use and safety of semaglutide

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Provenance: This is a Guest Editorial commissioned by Section Editor Dr. Kaiping Zhang, PhD (AME College, AME Group, Hangzhou, China).

Comment on: Aroda VR, Bain SC, Cariou B, *et al.* Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. Lancet Diabetes Endocrinol 2017;5:355-66.

Submitted Jan 17, 2018. Accepted for publication Jan 26, 2018.

doi: 10.21037/atm.2018.01.35

View this article at: http://dx.doi.org/10.21037/atm.2018.01.35

Long-term control of type 2 diabetes mellitus (hereafter simply diabetes) by the pharmacological approach remains difficult in a significant number of cases, despite the availability of a variety of anti-diabetes drugs and insulin preparations. Besides lowering blood glucose levels, control of body weight and prevention of hypoglycemia episodes are also important for better overall long-term management of type 2 diabetes (1,2).

Insulin glargine is a widely long-acting basal insulin preparation that is an add-on treatment option in patients with type 2 diabetes who are inadequately controlled with metformin alone (3). However, insulin induces weight gain via increasing energy intake, reducing glycosuria, and exerting central nervous effects (4). This weight gain and some other effects of insulin therapy may potentially worsen cardiovascular risk (5).

The incretin, glucagon-like-peptide-1 (GLP-1), contributes to plasma glucose homeostasis by promoting insulin release in a glucose-dependent manner, inhibiting glucagon release, and exerting various extra-pancreatic effects (6). GLP-1 receptor agonists (GLP-1RAs) have been increasingly widely used to treat diabetes, because they are associated with a lower risk of hypoglycemia and induce body weight loss (7). Pre-clinical basic studies have also suggested that GLP-1RAs protect pancreatic beta cells against beta cell damage and expand the pancreatic beta cell mass (8). Liraglutide, a GLP-1RA, was approved for the treatment of obesity by the U.S. Food and Drug Administration (FDA) in 2014 and by the European Medicines Agency (EMA) in 2015 (9). Semaglutide, a once-weekly GLP-1RA, was developed from liraglutide in the context of duration of action, stimulation of insulin secretion, and inhibition of food intake (10,11). Several recent lines of evidence indicate the promise of semaglutide for better diabetes care (12-18).

Metformin is the first-line medication usually prescribed for type 2 diabetes in the US. When metformin alone, or a combination of metformin plus sulfonylurea proves inadequate, the efficacy and safety of other add-on antidiabetic agents need to be considered. Recently, Aroda *et al.* reported a results of SUSTAIN-4 (NCT02128932), a 30-week, phase III randomized controlled, non-inferiority, multicenter, multinational trial conducted to investigate the efficacy and safety of semaglutide versus insulin glargine in insulin-naïve type 2 diabetes patients showing in adequate glycemic control with metformin alone or a combination of metformin plus sulfonylurea (15). A total of 1,089 participants were randomized to receive 0.5 mg of semaglutide (n=362), 1.0 mg of semaglutide (n=360), or insulin glargine (n=360) in the modified intention-to-treat population (mITT). In all the participating patients, the metformin or metformin plus sulfonylurea treatment was continued throughout the trial. Participants assigned to insulin glargine were started with the drug at the dose of 10 IU per day, with the dose subsequently titrated according to need. The primary endpoint was change in the mean HbA1c from baseline to week 30, and the secondary endpoint was the mean body weight change during the trial. Because

first-line therapy often fails to yield adequate diabetes control in a considerable number of diabetes patients, this study seems to be relevant for daily clinical practice.

In the SUSTAIN-4 trial, by week 30, the mean HbA1c (mean HbA1c at baseline 8.17%) decreased by 1.21% (95% CI, 1.10–1.31%) in the 0.5-mg semaglutide group, by 1.64% (95% CI, 1.54–1.74%) in the 1.0mg semaglutide group, and by 0.83% (95% CI, 0.73–0.93%) in the insulin glargine group. The mean dose of insulin glargine at the end of the study period in the insulin glargine group was 29.2 IU/day. The proportions of patients in whom the HbA1c values decreased to less than 7% or 6.5% were higher in the semaglutide groups than in the insulin glargine group (P<0.0001 for both). Furthermore, the percentages of participants in whom the HbA1c decreased to less than 7% in the absence of hypoglycemia episodes or weight gain were also significantly higher in the semaglutide groups as compared to the insulin glargine group (P<0.0001 for both). The mean fasting blood glucose and the plasma glucose in the 8-point self-testing of plasma glucose were significantly lower in the 1.0-mg semaglutide group as compared to the insulin glargine group. These data suggest that semaglutide provides better glycemic control than insulin glargine, in the absence of any risk of hypoglycemia.

In regard to the body weight changes in the same trial, by week 30, the 0.5-mg semaglutide group showed a body weight loss of 3.47 kg (95% CI, 3.00–3.93 kg) and the 1.0-mg semaglutide group showed a body weight loss of 5.17 kg (95% CI, 4.71–5.66 kg) (baseline body weight 93.45 kg). By contrast, the insulin glargine group showed a body weight gain of 1.15 kg (95% CI, 0.70–1.61 kg). The decreases in the BMI and waist circumference were also greater in the semaglutide groups as compared to the insulin glargine group. Since the baseline BMI was around 33 kg/m^2 in this study, reduction in body weight following treatment with semaglutide warrants consideration in severely obese patients under metformin treatment. Significant decreases of the blood pressure and serum levels of low-density lipoprotein (LDL) cholesterol, very low-density lipoprotein (VLDL) cholesterol, triglycerides, C-reactive protein and plasminogen activator inhibitor-1, and an increase of the pulse rate were also observed at week 30 in the semaglutide groups as compared to the insulin glargine group. The SUSTAIN-6 trial showed protective effects of semaglutide against cardiovascular events (16); thus, semaglutide, in addition to providing favorable glycemic control and weight loss, also seems to exert multiple favorable effects on the cardiovascular risk profile. Regarding adverse events, nausea was the most frequently encountered adverse event in the semaglutide groups (21% in the 0.5-mg group and 22% in the 1.0-mg group) in the SUSTAIN-4 trial. The semaglutide-induced gastrointestinal adverse events were, however, mild or moderate in all cases. As for hypoglycemia, 4% of patients in the 0.5-mg semaglutide group and 6% of patients in the 1.0-mg semaglutide group showed severe symptoms of hypoglycemia or blood glucose-confirmed hypoglycemia, as compared to 11% of patients in the insulin glargine group. Furthermore, hypoglycemia events were significantly fewer in both the 0.5-mg and 1.0-mg semaglutide groups as compared to the insulin glargine group. Although strict titration of insulin glargine could have contributed, at least in part, to the higher rate of hypoglycemia events in the insulin group, the number of hypoglycemic episodes were nonetheless significantly fewer in the semaglutide groups.

The SUSTAIN-1 trial was conducted to compare the efficacy and safety of semaglutide monotherapy versus placebo in treatment-naïve type 2 diabetes patients (12). In that study, the 0.5-mg and 1.0-mg semaglutide groups showed a body weight loss of 3.7 and 4.5 kg, respectively (baseline body weight 91.9 kg) and incidence rates of nausea of 20% and 24%, respectively. The SUSTAIN-2 trial was conducted to compare the efficacy and safety of semaglutide versus sitagliptin in type 2 diabetes patients showing inadequate glycemic control with metformin, a thiazolidinedione or both (13). In that study, the 0.5-mg and 1.0-mg semaglutide groups showed a body weight loss of 4.3 and 6.1 kg, respectively (baseline body weight 89.5 kg), and an incidence rate of nausea in both groups of 18%. The SUSTAIN-3 trial was conducted to compare the efficacy and safety of 1.0 mg semaglutide versus 2.0 mg extended-release exenatide in type 2 diabetes patients (14). In that study, the 1.0-mg semaglutide group showed a weight loss of 5.6 kg from the baseline weight of 95.8 kg, and an incidence rate of nausea of 22%. These results are consistent with the results of the SUSTAIN-4 trial, suggesting that the body weight loss and nausea in patients receiving treatment with semaglutide are independent of the patient background profile, stage of diabetes, or previous treatment received for diabetes in moderately obese type 2 diabetes patients. Because the BMI in Asian subjects, even those with diabetes, is generally lower than that in Caucasians, would the effects of semaglutide on weight loss and nausea differ in lean, Asian type 2 diabetes patients? The Japanese study in which the efficacy and safety of 0.5 or 1.0 mg semaglutide monotherapy were compared with those

of 100 mg sitagliptin partially answered that question (18). In that study, the 0.5-mg and 1.0-mg semaglutide groups showed a body weight loss of 2.2 and 3.9 kg from the baseline weight of 69.3 kg and incidence rates of nausea were 10.7% and 12.7%, respectively. The mean HbA1c (baseline value 8.1%) decreased by 1.9% and 2.2% in the 0.5-mg and 1.0-mg semaglutide groups, while it decreased by 0.7% in the sitagliptin treatment group. The reduction in body weight and incidence rate of nausea seemed to be somehow attenuated in Japanese type 2 diabetes patients, even though they showed larger reductions of the HbA1c value. A meta-analysis indicated that GLP1-RAs cause greater decreases of the HbA1c in Asian populations than in non-Asian populations (19). These results might reflect the difference in the effects of GLP1-RAs on insulin secretion and the insulin secretion capacity in Japanese non-obese patients with type 2 diabetes, which is characterized by reduced insulin secretion with beta cell dysfunction, but lower degrees of insulin resistance (20).

The weight loss induced by treatment with semaglutide is reported to be due to reduction in energy intake, less hunger and food cravings, better control of eating, and a lower preference for high-fat foods (21). The body weight loss in these patients is caused more by decrease of the body fat mass than by reduction of the body lean mass. Interestingly, in obese subjects treated with semaglutide, first-hour gastric emptying after a meal was delayed and the fasting and postprandial peptide YY responses were significantly lower (22). Obese subjects treated with semaglutide also had lower postprandial serum levels triglyceride, VLDL, and ApoB-48 after a standardized fat-rich breakfast (22). Hence, the effects of semaglutide on the gastro-endocrine system, central nervous system, and/or lipid metabolism might be responsible for the therapeutic benefit afforded by the drug in terms of weight loss and cardiovascular protection. Since the regulation of pancreatic beta cell function and mass is also crucial for the control of human type 1 and type 2 diabetes (23,24), investigation into the impact of semaglutide on the beta cell function and mass is warranted to evaluate unexplored potential in the field of diabetes and obesity treatment. In fact, first-phase (0–10 min) and second-phase (10–120 min) insulin secretion in the intravenous glucose tolerance test (GTT), maximal insulin capacity in the arginine stimulation test, and insulin secretion rate in the graded glucose infusion test were significantly increased in type 2 diabetes patients receiving semaglutide treatment (25).

As shown by the SUSTAIN trials, fewer hypoglycemia events occur in patients treated with semaglutide. Since no changes were observed in the plasma concentration-time curves of metformin, warfarin, atorvastatin and digoxin in healthy subjects who were receiving these drugs concomitantly with semaglutide (26), semaglutide appears to show no direct interactions with other anti-diabetes drugs. However, GLP-1RAs further potentiate insulin secretion induced by sulfonylureas from the pancreatic beta cells. When semaglutide is used in combination with a sulfonylurea or other hypoglycemic agents, the risk of hypoglycemia episodes should be considered, particularly in elderly patients or patients with renal or hepatic dysfunction.

Patients with diabetes are at a high risk of developing renal and hepatic dysfunction because of hyperglycemia and frequent association with hyperlipidemia, hypertension, obesity, insulin resistance, hormonal dysregulation, and/or chronic inflammation. In one study, the pharmacokinetics and tolerability of 0.5 mg semaglutide were evaluated in subjects categorized into various levels of renal function by the creatinine clearance level: normal renal function, mild, moderate or severe renal dysfunction, and end-stage renal disease (ESRD) (27); exposure to semaglutide was similar among the subjects with normal renal function, mild/moderate renal function impairment and ESRD, but 22% higher in subjects with severe renal impairment; however, all comparisons were within the pre-specified "no effect" limits after adjustments for differences in the age, sex and body weight. The creatinine clearance was not correlated with the semaglutide exposure or maximum plasma drug concentration in any of the subject categories. Furthermore, the pharmacokinetics of semaglutide was not affected by hemodialysis. In another study, the pharmacokinetics and tolerability of 0.5 mg semaglutide were assessed in subjects categorized into various levels of hepatic function level according to the Child-Pugh criteria: normal hepatic function, and mild, moderate or severe hepatic dysfunction (28). Semaglutide exposure and the maximum plasma concentrations were similar among all the aforementioned groups. These aforementioned findings indicate that semaglutide might be an ideal treatment agent for type 2 diabetes patients with renal or hepatic function impairment.

Semaglutide was developed as a tablet formulation using sodium N-[8-(2-hydroxybenzoyl) amino] caprylate (SNAC) and is thought to be absorbed via the transcellular route (29). The efficacy of oral/subcutaneous semaglutide was assessed by administration of once-daily oral semaglutide at 2.5, 5, 10, 20, 40 mg/4 weeks dose escalation, 40 mg/8 weeks dose escalation or 40 mg/2 weeks dose escalation, oral placebo

or once-weekly subcutaneous semaglutide at 1.0 mg to type 2 diabetes patients for 26 weeks (29). Oral semaglutide reduced the mean HbA1c by 0.7–1.9%, while the HbA1c decreased by 0.3% in the placebo-treated group and by 1.9% in the patients treated with subcutaneous semaglutide once weekly. Oral semaglutide and subcutaneous semaglutide reduced the body weight by 2.1–6.9 kg and 6.4 kg, respectively (baseline body weight, 92.3 kg), which were both greater than the weight loss observed in the placebo group (1.2 kg). Oral semaglutide at doses of 10 mg or more showed a significantly greater effect on weight loss as compared to placebo. In regard to the incidence rates of nausea, 13% to 37% of patients treated with oral semaglutide, 32% of patients treated with subcutaneous semaglutide, and 1% of patients treated with placebo developed nausea. Consequently, the efficacy and safety of oral semaglutide were comparable to those of subcutaneous semaglutide, even though higher doses are required for oral administration than for subcutaneous administration. Data on the effects of long-term administration of oral semaglutide are expected to be published in the near future.

On the basis of the SUSTAIN trials and other clinical studies, it may be concluded that semaglutide offers promise for providing better glycemic control and metabolic control with weight loss in patients with type 2 diabetes. As compared to the existing GLP-1RAs, semaglutide is likely to have greater merits, as demonstrated by the SUSTAIN-3 and SUSTAIN-7 trials (14). Oral semaglutide use might preclude the need for the inconvenient injection therapy in type 2 diabetes patients. In every study reported, the most common reason for discontinuations of semaglutide is gastrointestinal adverse events, especially nausea. Clarification of the precise mechanisms underlying the actions of semaglutide, including those underlying the development of the gastrointestinal adverse effects, would pave the way for the development of an appropriate therapeutic strategy with semaglutide for sustainable management of type 2 diabetes.

Acknowledgements

None.

Footnote

Conflicts of Interest: J Shirakawa has received lecture fees from Sumitomo Dainippon Pharma, Eli Lilly Japan K.K., MSD K.K., Mitsubishi Tanabe Pharma, Nippon Boehringer Ingelheim, Novo Nordisk, Sanofi K.K., Taisho Toyama Pharmaceutical, and Takeda Pharmaceutical Company, and grants from MSD K.K., Mitsubishi Tanabe Pharma, and Novartis Pharma; Y Terauchi has received honoraria for speakers bureau from Astellas Pharma, AstraZeneca K.K., Bayer Yakuhin, Daiichi Sankyo, Sumitomo Dainippon Pharma, Eli Lilly Japan K.K., Kowa, MSD K.K., Mitsubishi Tanabe Pharma, Nippon Boehringer Ingelheim, Novo Nordisk, Ono Pharmaceutical, Sanwa Kagaku Kenkyusho, Sanofi K.K., Shionogi & Company, Taisho Toyama Pharmaceutical, and Takeda Pharmaceutical Company, and grants from Astellas Pharma, AstraZeneca K.K., Bayer Yakuhin, Daiichi Sankyo, Sumitomo Dainippon Pharma, Eli Lilly Japan K.K., Kowa, MSD K.K., Mitsubishi Tanabe Pharma, Nippon Boehringer Ingelheim, Novo Nordisk, Ono Pharmaceutical, Pfizer Japan, Sanwa Kagaku Kenkyusho, Sanofi K.K., Shionogi & Company, and Takeda Pharmaceutical Company. He was an investigator in the Japanese phase IIIa trial of semaglutide.

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Cite this article as: Shirakawa J, Terauchi Y. SUSTAINable management of type 2 diabetes: feasibility of use and safety of semaglutide. Ann Transl Med 2018;6(7):129. doi: 10.21037/atm.2018.01.35

