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Clinical Improvement of Weight, HbA1c and Liver Function by Rybelsus (Oral Semaglutide) In Patient with Type 2 Diabetes (T2D), Obesity and Fatty Liver

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Abstract

Background: As glucagon-like-peptide 1 receptor agonist (GLP1-RA), oral semaglutide (Rybelsus) has been latest topic.
Case presentation: Patient is 72-year-old male with T2D, obesity, fatty liver and hypertension. He showed BMI 32.4 kg/m^2 and HbA1c 8.1% in Nov 2021.
Results: He started Rybelsus 3-7mg/day, and HbA1c and weight decreased for 8.1% to 7.0% and 92kg to 86.5kg with ALT/GGT improvement without gastrointestinal adverse events (GIAEs).
Discussion: This case has arteriosclerotic cardiovascular disease (ASCVD). From cardiovascular outcome trials (CVOTs), semaglutide group revealed lower odd ratio (OR) for less CV death, as 0.47 of exenatide, 0.46 of dulaglutide and 0.43 of lixisenatide.

Keywords: *Semaglutide (Rybelsus); Gastrointestinal adverse events (GIAEs); Glucagon-like-peptide 1 receptor agonist (GLP1-RA); Sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC); Semaglutide Treatment Effect in People with Obesity (STEP); Peptide InnOvatioN for Early diabEtes tReatment (PIONEER)*

Introduction

Concerning diabetes, incretin system has recently attracted attention. Glucagon-like peptide-1 (GLP-1) has been crucial hormone which inhibits glucagon release and regulates insulin secretion. For type 2 diabetes (T2D), GLP-1 receptor agonist (GLP-1RA) has been used as a beneficial therapeutic strategy [1]. Semaglutide is one of the GLP-1Ras, and became the first agent for possible oral administration once a day. It was approved by the Food and Drug Administration (FDA) of United States and it has been rather prevalent in clinical practice.

From historical point of view, orally administered peptide has been extremely challenging. It was from significant barriers of the bioavailability and stability in human gastrointestinal (GI) tract as well as variable pharmacokinetics [2]. By continuous research of drug delivery technology in Novo Nordisk for 30 years, oral semaglutide (Rylelsus®) has been approved by FDA as well as EMA and PmDA [3,4]. Fundamental experiments and applied research have continued as clinical trials of PIONEER. It stands for Peptide InnOvatioN for Early diabEtes tReatment (PIONEER) [5].

For standard management for diabetes, American Diabetes Association (ADA) has announced the medical care guideline in Jan 2022 [6]. Among them, pharmacological approaches have been summarized [7]. They include novel agents such as sodium–glucose cotransporter 2 inhibitor (SGLT2i), and GLP1-RA [8]. In several types of GLP-1Ras, oral semaglutide (Rybelsus) has showed crucial development of novel route of administration [9]. Authors and collaborators have presented T2D patient treated by Rybelsus associated with significant clinical efficacy [10]. Recently, we have a T2D case with impressive clinical progress,

and the general information and discussion will be described in this article.

Case Presentation

History and Physicals

The patient is a 72-year-old male patient with type 2 diabetes (T2D). As to his medical history, he was diagnosed as hypertension at the age of 60 years old in 2010. After that T2D and fatty liver was diagnosed in 2012 and 2013, respectively. He had bilateral shoulder periarthritis in 2016, and degenerative lumbar spondylosis in 2018. His diabetic control had been rather stable for 6.8% to 7.5% of HbA1c until July 2021. However, the HbA1c increased to 8.1% in autumn 2021. His weight were between 90-92kg until then (Figure 1).

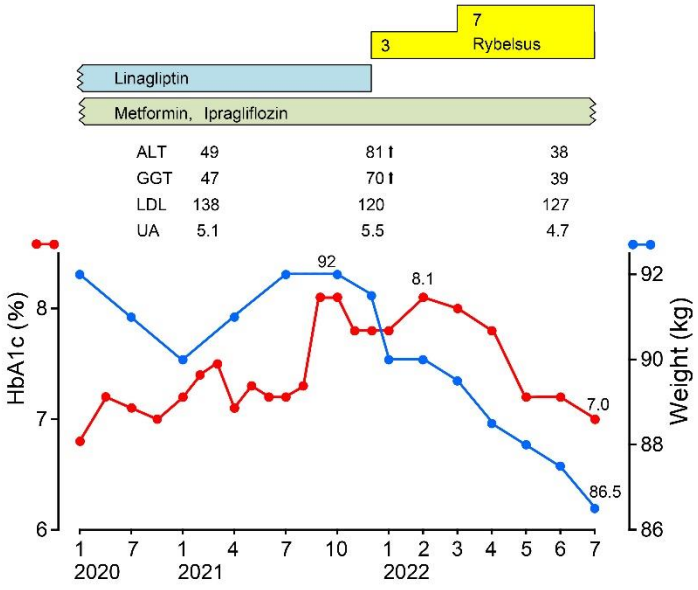

Figure 1: *Clinical progress for HbA1c, weight and laboratory data.*

His physicals in Nov 2021 were as follows: consciousness alert, speech and vitals are normal, his lung, heart, abdomen and neurological situations were unremarkable. His physique was 168.5 cm, 92.0 kg, BMI 32.4 kg/m^2.

Several examinations

His blood tests in Nov 2021 were in the following: ALT 34 U/L, ALT 80 U/L, LDH 241 U/L (124-222), GGT 70 U/L, LDL-C 120 mg/dL, TG 260 mg/dL, HDL-C 42 mg/dL, BUN 19 mg/dL, Cr 0.86 mg/dL, UA 5.5mg/dL, WBC 9600 /μL, RBC 5.45 x 10^6/μL, Hb 16.2 g/dL, Ht 52.1 %, MCV 95.6 fL, MCH 29.7 pg, MCHC 31.1 g/dL, Plt 25.7 x 10^4 /μL, post-prandial blood glucose 227 mg/dL and HbA1c 8.1 %.

Other examinations were performed during autumn 2021 to spring 2022. Chest X-P revealed unremarkable findings, and Electrocardiogram (ECG) showed negative results without ST-T changes. He had received the exam for peripheral artery disease (PAD). As a result, ankle brachial index（ABI）revealed 1.23/1.19 in right/left. The values of brachial-ankle pulse wave velocity (baPWV) were 1879/1902 for right/left, respectively. The result of mechanocardiogram (heart function diagram) and sphygmogram (pulse wave chart) is shown in Figure 2. They revealed normal ranges of % mean arterial pressure (%MAP) and upstroke time (UT).

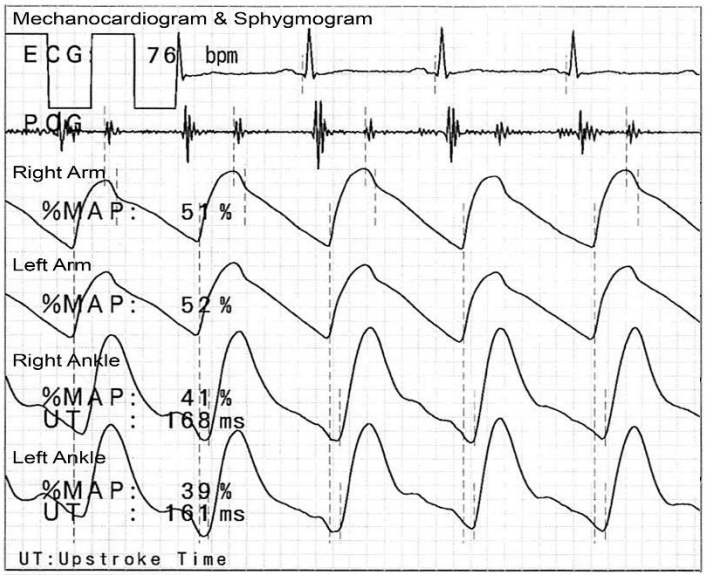

Figure 2: *The CV results of mechanocardiogram and sphygmogram.*

Clinical progress

This case showed elevated values of HbA1c, ALT, GGT associated with weight gain in Nov 2021. Then, he was advised to initiate oral semaglutide from Dec 2021 that was Rybelsus 3mg/day in early morning. This dose was continued for 16 weeks and increased to 7mg/day after that. His HbA1c and weight have gradually decreased, and he showed HbA1c 7.0% and body weight 86.5kg in July 2022. His clinical progress of HbA1c, weight, liver function, LDL, Uric acid and medication is summarized in Figure 1.

Ethical Considerations

This study was fundamentally conducted with the principles of the ethics for the Declaration of Helsinki. Furthermore, certain commentary was along with the Ethical Guideline for Human Research. These are consistent with the Good Clinical Practice (GCP). Authors and co-researchers established the ethical committee for this study. The committee is present in our hospital with several professional members. They are the director of the hospital, physician, pharmacist, nutritionist, and legal specialty. For the committee meeting, enough discussion was performed. As

a result, satisfactory agreement was obtained according to the protocol. The document for the informed consent was provided from the patient.

Discussion

Oral semaglutide has been evaluated to be useful and beneficial agent for the treatment of T2D and obesity as Rybelsus [11]. It was synthesized by the pharmacological development with absorption enhancer, that is sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC) [12]. It became the cornerstone for historical pharmaceutical situation, because the peptide can be administered per os [13]. Furthermore, oral semaglutide revealed cardiovascular (CV) efficacy and safety, and showed the similar situation compared with subcutaneous administration [14]. Consequently, SNAC may be one of the drastic agent for future drug delivery system (DDS) [15].

For our actual medical practice, some GLP-1RAs have been used [16]. Their types were classified in the following: a) oral semaglutide once daily for novel type of formulation, b) subcutaneous once weekly as semaglutide, duraglutide and exenatide, c) subcutaneous twice a day as exenatide, and d) subcutaneous once daiy: lixenatide and liraglutide. Among these kinds of administration, oral intake seemed to be simple and useful. From clinical effect point of view, oral semaglutide has contributed improvement of T2D and also obesity [17]. Large clinical studies were conducted for Rybelsus, including Peptide InnOvatioN for Early diabEtes tReatment (PIONEER) and Semaglutide Treatment Effect in People with Obesity (STEP) [8]. They revealed that the agent has gastrointestinal adverse events (GIAEs), but the degree was not so severe.

In this case, 72-year-old male patient has showed gradual elevation of body weight, HbA1c, liver function of ALT and GGT for a few years. He has medical problems including T2D, fatty liver, hypertension and orthopedic arthralgia. For the purpose of his treatment, the improvement of T2D and obesity would be indispensable. Consequently, oral semaglutide (Rybelsus) was suitable agent. As a matter of fact, his weight and HbA1c were decreased enough for short period, indicating satisfactory clinical efficacy. He did not feel any GIAE. He can tolerate Rybelsus well associated with general improvement. Like this case, T2D patients often have obesity and fatty liver, and then Rybelsus may contribute clinical improvement of these problems [18].

This case has T2D and hypertension, which indicates the existence of arteriosclerotic cardiovascular disease (ASCVD). Concerning ASCVD and semaglutide, seven cardiovascular outcome trials (CVOTs) were investigated. It included 56 thousand cases, and semaglutide group revealed lower odd ratio (OR) for less CV death [19]. The data showed 0.47 of exenatide, 0.46 of dulaglutide, 0.45 of albiglutide and 0.43 of lixisenatide. These results suggested the beneficial efficacy of semaglutide for ASCVD. Another report was found as to 9890 cases from 11 RCTs. They showed the superior clinical effect of semaglutide than other GLP-1Ras [20]. As a result, the difference of weight and HbA1c was 1.48kg and 0.35%, compared with empagliflozin, liraglutide and sitagliptin groups. Actual reduction data in semaglutide group were 2.99kg and 0.89%, respectively which were satisfactory degree. When this predominance was calculated for OR, which showed OR 0.55 in CV mortality and OR 0.58 in all-cause mortality.

Clinical efficacy of semaglutide for CV risk was shown from the data of PIONEER and SUSTAIN [21]. As to semaglutide group and comparator group, several factors were compared as hazard ratio (HR). There were 3 risk groups among them as higher 95%, middle 50%, lower 5%, in which HR was 0.84, 0.62, 0.45, respectively. For the middle CV risk, semaglutide vs comparator groups revealed the results: HbA1c 7.2% vs 10.3%, systolic blood pressure 137 mmHg vs 163 mmHg, LDL-C 124 mg/dL vs 151 mg/dL, eGFR 91.7 mL/min/1.73m^2 vs 94.1 mL/min/1.73m^2, respectively. Thus, semaglutide group showed lower risk of major adverse cardiovascular events (MACE) in the T2D cases [21].

Some limitation may be found in the case report. This is only one case with T2D, obesity and fatty liver, who took oral semaglutide. He showed satisfactory clinical improvement of weight and HbA1c, without any GIAEs. However, longer clinical progress will be followed up from several points of view in the course. They include T2D, body mass index (BMI), liver function tests, renal function, macroangiopathy of cerebral vascular accident (CVA), CVD and peripheral artery disease (PAD) [22]. In summary, elder male revealed remarkable improvement of weight and HbA1c, liver function by oral semaglutide (Rybelsus). This report is expected to be a useful reference, beneficial to diabetic research and practice in the future.

Conflict of Interest

The authors declare no conflict of interest.

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