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Efficacy for Reduction of HbA1c and Body Weight by Oral Semaglutide (Rybelsus)

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Abstract

Background: Oral semaglutide (Rybelsus) has been recently in focus for type 2 diabetes (T2D).
Case presentation: Case is 61-year-old female with T2D, obesity, fatty liver and Gastro Esophageal Reflux Disease (GERD). Her HbA1c was 13.2% in Dec 2021, and she started to have metformin, empagliflozin and Rybelsus from 3mg to 7mg/day. General situation was improved as -4.2% of HbA1c and -8kg in weight for 4 months.
Discussion and Conclusion: This case has GERD, and then the doses of Rybelsus kept 7mg/day. She did not feel any gastrointestinal adverse effects (GIAEs). This impressive case will become reference for diabetic practice.

Keywords: *Oral semaglutide (Rybelsus); Type 2 diabetes (T2D); Gastro Esophageal Reflux Disease (GERD); Gastrointestinal adverse effects (GIAEs); Sodium N-[8-(2-hydroxybenzoyl) amino] caprylate (SNAC)*

Introduction

Medical and social problems of obesity and diabetes have been more in focus in developed and developing countries [1]. These situation may cause unsatisfactory activity of daily livings (ADL) and quality of life (QOL) [2]. Especially, patients with type 2 diabetes (T2D) have been more found who are more than 60s and 70s [3]. T2D includes various diabetic complications such as microangiopathy, macroangiopathy, sarcopenia and other impaired functions [4]. As to adequate diagnosis and treatment of T2D, latest guideline for standard diabetic care was announced by American Diabetes Association (ADA) in January 2022 [5]. Recommended level of adequate glucose control has been presented for a various situation of diabetic patients [6].

As regard to diet therapy, calorie restriction (CR) was formerly standard method. After that, low carbohydrate diet (LCD) method was introduced to medical and health care region [7]. Consequently, actual LCD continuation have been understood and prevalent across the world [8]. Authors et al. started and developed LCD socially through the activity of Japan LCD promotion association (JLCDPA) [9]. We proposed useful LCD method including super-, standard- and petite-LCD [10].

Concerning pharmacological therapy, ADA proposed the recent standard treatment in the guideline [11]. They include several agents such as glucagon-like-peptide 1 receptor agonist (GLP1-RA) [12,13] and sodium–glucose cotransporter 2 inhibitor (SGLT2i) [11,14]. Among them, oral semaglutide (Rybelsus) has attracted attention, that was introduced to medical practice [15]. The important point would be the novel route that not only injection but also oral route become possible [16]. Authors and collaborators in diabetic medical team have so far continued several reports about glucose variability and oral hypoglycemic agents (OHAs) [17,18]. Some cases have applied oral semaglutide, who showed rather satisfactory clinical efficacy [19,20]. In this article, we present an impressive case treated with oral semaglutide.

Case Presentation

History & Physical

The patient is a 61-year-old female patient with T2D. She was diagnosed as T2D about 12 years ago, and has been treated by some OHAs for 4 years. Her OHAs included metformin 1000mg and Vildagliptin 100mg/day from 2018. Her HbA1c was stable, but gradually increased to 8.8% in July 2019. She was started to be given Empagliflozin 25mg/day. After that, her HbA1c has decreased 7.0% in March 2021. However, her family had various problems including her father's death and others during summer to autumn 2021. Such situation brought her not to visit diabetic clinic for several months (Figure 1).

Concerning her physical examination, her consciousness, speech and vital signs are normal. Her stature has been 164 cm and her body weight 83kg in Jan 2021 with body mass index (BMI) 31.2 kg/m^2. This value of BMI means 1 degree of obesity from international guideline. She showed unremarkable findings of lung and heart. Her abdomen is distended, soft with normal range of bowel sound. No significant neurological abnormality was found.

Several exams

The biochemical and other results of Jan 2021 were summarized as follows: GOT 48 U/L,GPT 52 U/L, GGT 61 U/L, AlP 231 (100-340), LDH 163 U/L (120-240), LDL-C 115 mg/dL, TG 211 mg/dL, HDL-C 42 mg/dL, BUN 11 mg/dL, Cr 0.76 mg/dL, eGFR 66 mL/min/1.73m^2, UA 5.2 mg/dL, Na 141 mEq/L, K 4.5 mEq/L, Cl 100 mEq/L, RBC 4.57 x 10^6 /μL, Hb 13.9 g/dL, MCV 83.8 fL, MCH 30.4 pg, MCHC 36.2 g/dL, WBC 7000 /μL, Plt 27.5 x 10^4 /μL, serum Fe 90 μg/dL, TIBC 364 μg/dL, UIBC 274 μg/dL, ferritin 74 ng/mL. For several tests for DM, post-prandial blood glucose 214 mg/dL, HbA1c 7.5 %, urinalysis findings were presented as protein (-), glucose (++), urobilinogen (+/-), ketone body (+). Chest X-P was normal for heart and lung, and Electrocardiogram (ECG) revealed within normal limits. Occult blood in stool was negative, and other remarkable findings were not detected.

Clinical progress

After several month absence, she visited our clinic again in Dec 2021. Her HbA1c and 30-min post-prandial glucose were 13.2% and 506 mg/dL, and body weight was 85 kg. Our medial team has consulted with the patient concerning the detail situation, and come to judge probably successive cooperative and stable treatment progress. Consequently, she was started to be given Rybelsus 3mg as oral semaglutide from Dec 2021.

She could take Rybelsus 3mg satisfactory for 4 weeks. In Jan 2022, Her HbA1c and 30-min postprandial glucose after breakfast were 12.3% and 228mg/dL. Rybelsus was increased from 3mg to 7mg, and 7mg was continued after that. In Feb 2022, her HbA1c and 30-min post-prandial glucose was 234 mg/dL, with body weight 82kg. Thus, after increasing the dose of Lybersus, HbA1c decreased from 13.2% to 7.7% and the body weight decreased from 85 kg to 77 kg (Figure 1).

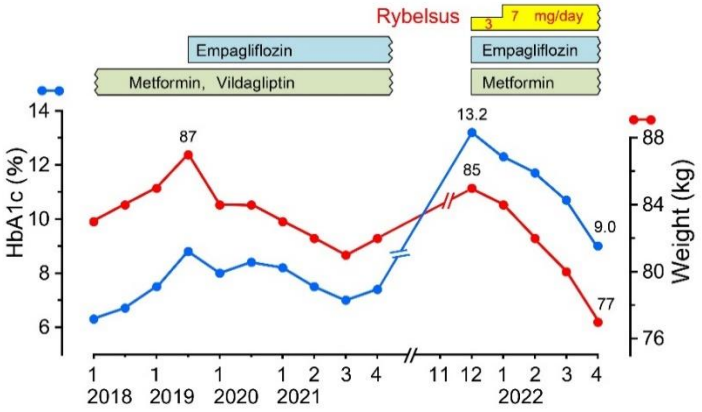

Figure 1: *Clinical progress with changes in HbA1c and body weight for oral semaglutide.*

Medical problems

According to the obtained data of history, exams and clinical course, medical problems would be summarized as follows. They are #1 obesity, #2 T2DM, #3 Gastro Esophageal Reflux Disease (GERD) and #4 fatty liver. Concerning her medication so far, she has continued metformin 1000mg and empagliflozin 25mg per day and recently Rybelsus 3mg, 7mg (#2), and Lansoprazole 15mg per day for years (#3). Oral semaglutide shows clinical effect on #1 and #4.

Ethical Review

Current study was performed in compliance with the Declaration of Helsinki, which was revised at WMA Fortaleza General Assembly in 2013. Furthermore, it was along with the ethical guidelines for human-based medical research that was notified by Ministry of Education, Culture, Sports, Science and Technology [MEXT] and also Ministry of Health, Labour and Welfare [MHLW]. The protocol and examination were explained to the patient in advance. Concerning this project, a consent form was obtained from the case. This study was discussed and obtained the approval of the Ethics Review Committee of Yoshinogawa hospital. The committee included the director, physician, head nurse, pharmacist, and legal professional.

Discussion

In recent years, GLP-1Ras have attracted attention in diabetic practice. Among them, semaglutide was developed for the first novel oral agent after long years of research continuation [21]. It became possible for pharmacological invention for the co-formulation of the peptide associated with the sodium N-[8-(2-hydroxybenzoyl) amino] caprylate (SNAC) [22]. By the function of SNAC, the difficult situation concerning the absorption of

semaglutide peptide in strong acidic fluid in the stomach could be overcome. For medical effect of Rybelsus, cardiovascular safety was observed as non-inferiority compared with placebo group [23]. Consequently, evolutionary process of oral intake can lead more beneficial treatment for many patients with T2D.

Semaglutide has been studied in various kinds of trials. As a novel aspect, it has two route possible agent including by injection and also per os. The well-known projects include three categories, which are i) SUSTAIN (Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes), ii) STEP (Semaglutide Treatment Effect in People with Obesity) and iii) Peptide InnOvatioN for Early diabEtes tReatment (PIONEER). As for these trials, detail contents show i) once-weekly subcutaneously administration of 1.0 mg, ii) once-weekly subcutaneously 2.4mg, and iii) oral administration. From various results of these studies, semaglutide showed the similar efficacy of glucose variability and satisfactory weight reduction in comparison with other anti-diabetic agents [24].

Among several investigations of PIONEER, Japanese T2D patients were studied for their safety and effect in PIONEER 9 and 10 [25]. The protocol revealed the clinical study of using 3, 7, and 14mg of oral semaglutide (Rybelsus), subcutaneous dulaglutide and subcutaneous liraglutide for the period of 52 weeks. The results showed that 701 cases have shown clinical effect and not remarkable adverse events. Consequently, semaglutide of injestable and oral routes have showed clinical effects for patients with all ages.

For current case, we kept the doses of 7mg, and did not increase 14mg. It was because she has the problem of GERD. Our medical team do not usually increase Rybelsus dose abruptly. By explaining the detail characteristic of this agent, the patient was advised to take medicine along to our schedule. She can always keep certain fasting time period after taking Rybelsus about 60-90 minutes. As regard to the medication package insert of Rybelsus, 30-minutes fasting after administration would be the standard time period [15]. By regulating the fasting time for 30, 60, 120 minutes, the concentration in the blood can show much different. She could keep fasting time after meds rather long, and she could continue to take Rybelsus without any Gastrointestinal adverse effects (GIAEs).

The relationship between blood concentration of semaglutide and fasting time period after taking med was investigated [26]. The measured data could be obtained from the reported figures concerning concentration and time period. The semaglutide concentration would be compared in the case of 15, 30, 60, 120 minutes, respectively. When the standard concentration is estimated as 1.00 for 15 minutes, the ratio of semaglutide concentration after 4 hours taking med would be calculated as 1.67 (30 min), 2.60 (60 min) and 3.06 times (120 min), respectively [27]. In addition, water volume study showed no apparent changes between 50mL and 120mL that is taken simultaneously with Rybelsus [15]. These results revealed positive efficacy of semaglutide associated with SNAC for drug delivery system (DDS) [28]. Several recommended doses were shown from previous phase three clinical studies [29,30].

This case showed remarkable reduction of body weight and HbA1c by the administration of oral semaglutide. Her weight was 77kg in Apr 2020, which was most decreased level so far. She was planned to be followed up, but her successive clinical management was transferred to another clinic due to her family situations. Some limitations may exist in the current case. She has several medical problems of T2D, obesity, fatty liver and GERD. From gastro-intestinal function, this case kept 7mg of Rybelsus and did not reveal GIAEs. In summary, 61-year-old female with T2D received the treatment of oral semaglutide. She showed clinical improvement as -4.2% of HbA1c and -8kg in weight for 4 months, indicating satisfactory clinical efficacy. This article would hopefully provide some reference for diabetic research and practice.

Conflict of interest: The authors declare no conflict of interest.
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