



Significant Reduction of Body Weight and Blood Glucose by Oral Semaglutide (Rybelsus) for Type 2 Diabetes (T2D) Patient

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Abstract

Background: Recent topic for diabetes includes oral semaglutide (Rybelsus).

Case presentation: A Patient is 75-year-old female with Type 2 diabetes (T2D). Her HbA1c has been 6.8-7.6% for long, but increased to 8.4-8.8% in Jan 2022 with BMI 27.6 kg/m².

Results: She started Rybelsus 3-7mg/day, and then weight and HbA1c decreased as 7kg and 1.6% in 4 months.

Discussion: Rybelsus is known for improvement of weight and glucose variability. For her clinical effects, some probable reasons include '70s for age, less developed microangiopathy and macroangiopathy, longer fasting time period after Rybelsus intake. This case will become useful reference for diabetic research.

Keywords: Oral semaglutide (Rybelsus); Gastrointestinal adverse events (GIAEs); Semaglutide Treatment Effect in People with Obesity (STEP); Glucagon-Like Peptide 1 receptor agonist (GLP-1RA); Peptide InnOvation for Early diabetes treatment (PIONEER)

Introduction

Diabetes has been social and medical crucial problem, and the number of diabetic patients has been rapidly increasing worldwide [1]. Concerning adequate management of diabetes, American Diabetes Association (ADA) has announced latest guideline for standard medical care in Jan 2022 [2]. Especially, the management for elderly diabetic patients would be important from several points of view [3]. The problems of diabetes and obesity have been challenging aspects to be solved, and various trials have been reported until now [4].

As regards to anti-obesity agents, FDA of US has approved several meds, including phentermine/topiramate, naltrexone/bupropion, orlistat, liraglutide and semaglutide [4]. These agents can contribute to modulate appetite and satiety. Semaglutide treatment once-weekly showed clinical effect for obesity cases, but some gastrointestinal adverse events (GIAEs)

are observed. These data are found from the 1-3 trials of STEP (Semaglutide Treatment Effect in People with Obesity) and these influence for weight reduction were also analyzed [5].

Among Glucagon-Like Peptide 1 receptor agonists (GLP-1RAs), semaglutide has been attracted attention for broad beneficial clinical efficacy [6]. It has two types of injective administration and oral formulation [7]. Especially, oral semaglutide (Rybelsus) has been highly evaluated for the pharmacological technique for oral agent [8]. Further, the beneficial efficacy includes both of weight reduction and improved blood glucose variability [9]. Authors and colleagues continued clinical diabetic research for low carbohydrate diet (LCD), continuous glucose monitoring (CGM), GLP-1RA and others [10,11]. Concerning oral semaglutide, our research group have reported a diabetic case with remarkably improvement of weight and blood glucose [12]. We recently experienced a diabetic case who developed elevated

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weight and HbA1c, and relieved by Rybelsus. General outline and some discussion would be described in this article.

Case Presentation

History, Physical and exams

The patient is a 75-year-old Japanese female patient with Type 2 diabetes (T2D). She was diagnosed as T2D in 2009. After that, she has been provided some kinds of oral hypoglycemic agents (OHAs). For recent years, her HbA1c values persisted 6.8-7.6% and weight was stable about 58kg. For December 2021 to January 2022, her general condition became exacerbation with elevated HbA1c 8.4-8.8% and weight.

Her physique was 147.5cm in height and 60kg in weight with BMI 27.6 kg/m². Concerning her physical examination, her vitals, consciousness, speech and neurological findings were unremarkable. Furthermore, her heart, lung and abdomen showed negative findings. She showed a slight spontaneous pain in bilateral knees from osteoarthritis for years.

The blood biochemical results of Dec 2021 were as follows. They are AST 22 U/L, ALT 29 U/L, r-GT 48 U/L, ALP 60 U/L (38-112), LD 225 (124-222), LDL 74 mg/dL, TG 59 mg/dL, HDL 75 mg/dL, BUN 23 mg/dL, Cr 0.81 mg/dL, RBC 5.07 x 10⁶ /μL, Hb 14.6 g/dL, Ht 44.6 %, MCV 88.0 fL, MCH 28.8 pg, MCHC 32.7 g/dL, WBC 4700 /μL, Plt 23.4 x 10⁴ /μL, HbA1c 8.3 %, post-prandial blood glucose 214 mg/dL.

Several examinations were performed during July-December 2021 in the following. Chest X-ray and Electrocardiogram (ECG) were negative. For cardiovascular examination for peripheral artery disease (PAD), ankle brachial index (ABI) showed 0.97/1.25 with brachial-ankle pulse wave velocity (baPWV) in 2645/2593 (right/left), respectively. The results for the bone density test showed 106% for %AGE, 71% for % young adult mean (YAM) and bone density 0.461 g/cm², which were borderline results for 75-year-old female.

Medical Problems and Meds

From various situation and information, medical problems and medication can be summarized.

- **T2D:** Metformin 500mg, Canagliflozin 100mg, glimepiride 2mg, Miglitol 75mg/day, Teneligliptin Hydrobromide Hydrate (20mg) per day have been given until Dec 2021. From Jan 2021, teneligliptin as DPP4-I was discontinued and oral semaglutide (Rybelsus) was started from 3mg for 4 weeks and 7mg from 5 weeks.
- **Gastro Esophageal Reflux Disease (GERD):** The case has taken vonoprazan fumarate (Takecab) 10mg/day. Constipation: Magnesium oxide 1500mg, Lubiprostone (Amitiza) 48mg per day have been provided.

- **Dyslipidemia:** The patient has taken Rosuvastatin 2.5mg per day. Currently, LDL-C value is within normal limits.
- **Mild cognitive impairment (MCI):** The case has been pointed out to have slight level of MCI, but it does not influence her usual daily life so much. The medication is Donepezil Hydrochloride 10mg per day.
- **Osteoarthritis of the knee:** She has some pain in bilateral knees. She has occasionally used the plaster of Loxoprofen Sodium Hydrate for knees.

Results and Clinical Progress

Since her glucose variability became exacerbation in Jan 2022, she was started to be given Rybelsus 3mg/day for 4 weeks. Successively, Rybelsus dose was increased to 7mg/day. As a result, HbA1c was decreased from 8.8% to 7.2%, and body weight was also reduced from 58kg to 52kg (Figure 1). Consequently, the administration of 3 and 7 mg/day showed clinical efficacy for glucose metabolism and body weight. She did not develop any health or medical problems such as GIAEs.

Ethical Considerations

This study has been fundamentally conducted with principles of ethics from the Declaration of Helsinki. In addition, some comment was shown from the Ethical Guideline from the Research for Human point of view. They are along with the Good Clinical Practice (GCP). Authors and co-researchers established a related ethical committee for ethical considerations. The committee is present in our hospital which has several members of professional. The persons in charge are the director of the hospital, physician, surgeon, nutritionist, pharmacist, and legal specialty. In the committee, fully discussion was performed, and the agreements were given from the protocol of this study. The informed consent was provided with written agreement from the patient.

Discussion

Several types of GLP-1Ras have been used in clinical practice so far [13]. There are some categories in the following [14]. They are i) lixisenatide and liraglutide subcutaneous injection once a day, ii) exenatide subcutaneous injection two times a day, iii) semaglutide, exenatide and duraglutide subcutaneous injection once a week, and iv) oral semaglutide formulation which has been from the PIONEER (Peptide InnOvatioN for Early diabEtes tReatment) trials.

Among these GLP-1Ras, semaglutide is the first oral agent that was developed from continuing research for long years [15]. The crucial point would be the co-formulation of semaglutide and the novel caprylate of the absorption enhancer sodium N-(8-[2-hydroxybenzoyl] amino) [16,17]. The difficult situation was overcome by peptide absorption in the stomach with strong acid

presence by Novo Nordisk [18]. As to actual effect of Rybelsus, cardiovascular (CV) safety was proved to be non-inferiority to the placebo, and CV efficacy. Rybelsus showed similarity to subcutaneous semaglutide administration [19]. Consequently, this revolutionary oral hypoglycemic agent (OHA) of GLP-1RA will surely change the drug delivery system (DDS) in the future [20,21].

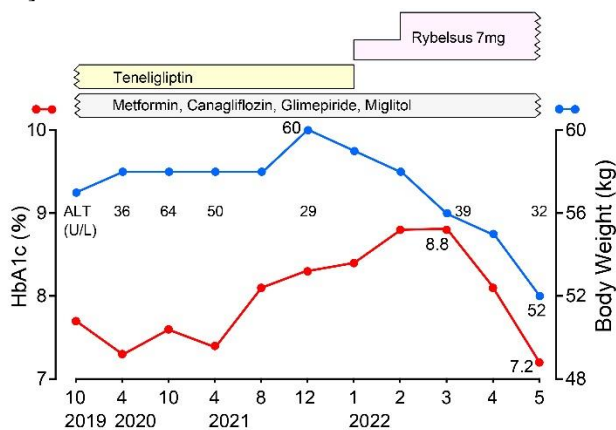


Figure 1: Clinical progress of the case.

In this case, significant improvement of body weight and blood glucose variability was found. Some comparative previous reports are observed. For oral semaglutide, systematic review was performed including 9890 cases and 11RCTs [22]. Compared with empagliflozin, sitagliptin and liraglutide, semaglutide showed the effective superiority of weight and HbA1c as -1.48kg and -0.35%, respectively. Actual average data were the improvement of weight 2.99kg and HbA1c 0.89%. In addition, clinical superiority was found for odds ratio (OR), in which all-cause mortality 0.58, cardiovascular mortality 0.55 and neutral effects for myocardial infarction, stroke, diabetic hypoglycemia and retinopathy. For another study of 7 cardiovascular outcome trials (CVOTs) for 56 thousand cases, semaglutide showed effective OR for less cardiovascular death, such as exenatide 0.47, dulaglutide 0.46, albiglutide 0.45 and lixisenatide 0.43 [23].

What kind of factors were involved in the significant clinical effects in this case? This patient is 75-year-old female with 13 years of diabetic history. She is in the '70s with stable QOL and ADL. The case has maintained HbA1c level about 6.8-7.6 % for years, and has not severe neuropathy, retinopathy, nephropathy or impaired pathology of brain, heart and legs. From these situations, the case seems to have less microangiopathy and macroangiopathy. Another factor may be the fasting time after intake of Rybelsus. The standard fasting time is 30 minutes. In contrast, this case always has 60-90 min of fasting. According to the previous report of phase 3 trial, blood concentration level of semaglutide increases when fasting time becomes longer [24]. When the fasting time is 15, 30, 60 and 120 minutes, the ratio of Area Under the Curves (AUC) of blood concentration would be

1.00, 1.87, 2.30, 3.05, respectively. Consequently, the fasting time period would be important for clinical efficacy. Furthermore, this case did not develop any adverse effect, although blood concentration was supposed to be higher [25].

Some limitation exists in this report. This is only one case report, and the effect of Rybelsus is not necessarily found in any diabetic patient. The case did not have so complicated diabetic complications or pathology. The age is in the '70 and fasting time was rather longer after intake of Rybelsus. Careful follow up the case would be required.

Conclusion

In summary, 75-year-old diabetic female showed significant reduction of body weight and blood glucose by oral semaglutide (Rybelsus). It is expected that various factors related to this case will become a reference for diabetic clinical practice and research.

Conflict of Interest

The authors declare no conflict of interest.

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