



Useful Oral Administration of Glucagon-Like Peptide 1 Receptor Agonist (GLP-1RA) as Semaglutide (Rybelsus) for Type 2 Diabetes Mellitus (T2DM)

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Abstract

As recommended pharmacological agents for type 2 diabetes mellitus (T2DM), Glucagon-Like Peptide 1 receptor agonist (GLP-1Ra) is highly evaluated for its various beneficial effects. Among them, semaglutide (Rybelsus) has been in focus for useful oral formation with useful oral hypoglycemic agent (OHA). Administration per os is possible due to the developed technique of absorption enhancer sodium N-(8-[2-hydroxybenzoyl] amino) caprylate. Clinical efficacy was shown by a series of Peptide Innovation for Early Diabetes Treatment (PIONEER) with enough weight reduction and decreased HbA1c. From the results of several PIONEER programs, oral semaglutide 14 mg/day had reduced HbA1c values by approximately 1.0-1.4%.

Keywords

Semaglutide, Rybelsus, Sodium N-(8-[2-hydroxybenzoyl] amino), Peptide Innovation for Early Diabetes Treatment (PIONEER), Semaglutide Treatment Effect in People with Obesity (STEP)

Abbreviations

PIONEER: Peptide Innovation for Early Diabetes Treatment; STEP: Semaglutide Treatment Effect in People with Obesity

Diabetes has been a syndrome by hyperglycemia from chronic impaired metabolism of carbohydrate, protein and fat. International Diabetes Federation (IDF) has continued worldwide management for long utilizing artificial neural network (ANN) [1]. American Diabetes Association (ADA) has announced the standard diabetic guideline on Jan 1, 2022 [2]. Their characteristic points include pharmacological review indicating clinical efficacy of Glucagon-Like Peptide 1

receptor agonist (GLP-1Ra) [3]. Authors and coresearchers have reported various diabetic research and practice with GLP-1RAs and glucose variability [4,5]. Several topics concerning GLP-1Ras and semaglutide (Rybelsus) will be described in this article.

In previous studies for GLP-1Ras, clinical effects were found for semaglutide, liraglutide, exenatide, dulaglutide and lixisenatide. These agents were given

through subcutaneous injection one daily or once weekly. GLP-1Ras have shown clinical efficacy for type 2 diabetes mellitus (T2DM) [6]. They include improving blood glucose profile and controlling body weight. Recently, semaglutide has a beneficial topic for administering the agent orally. Further, it has several clinical studies continuing for long [7]. They are i) Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN), ii) Peptide Innovation for Early Diabetes Treatment (PIONEER) and iii) Semaglutide Treatment Effect in People with Obesity (STEP) programs. Among them, semaglutide amount and route are i) 1.0mg subcutaneous once-weekly, ii) oral administration of novel GLP-1 homolog (3mg, 7mg, 14mg) and iii) 2.4mg subcutaneous once-weekly, respectively. From mentioned above, semaglutide showed clinically effects for weight loss and better glucose variability in comparison with other agents for T2DM.

Regarding medications for obesity, US FDA approved several agents so far, which are semaglutide 2.4mg, liraglutide 3mg, orlistat, naltrexone/bupropion extended release (ER) and phentermine/topiramate ER [8]. These agents contribute to improve the adherence to recommended diet as their principles, by modulating satiety and appetite. The treatment of semaglutide 2.4mg once-weekly has shown clinical efficacy for patients with obesity or overweight, but it has gastrointestinal adverse events (GIAEs). GIAEs data from the Semaglutide Treatment Effect in People with Obesity (STEP) 1-3 trials and their influence to weight loss (WL) were analyzed [9]. As a result, GIAEs were rather common with semaglutide vs placebo, as nausea 43.9% vs 16.1%, diarrhea 29.7% vs 15.9%, and constipation 24.2% vs 11.1%, in which most GIAEs were non-serious. During STEP 1-3, mean WL for semaglutide group was similar in cases without GIAEs vs with GIAEs, as 9.6-17.1% vs 11.4-17.7%, respectively. Thus, semaglutide-induced WL seems to be mostly independent of GIAEs.

From basic aspect of semaglutide, research advances were observed regarding the route of administration. For pharmacological point of view, majority of peptides are delivered are injected, while a few matters are delivered orally. The reason would be that

significant barriers are present for the absorption results, associated with variable oral bioavailability [10]. Among various researches for drug delivery system (DDS), there were lack of equivalence for gastrointestinal tract and mucosa between animal and human [11]. Successively, progress of DDS research enabled oral peptide formulation that is available for market [12]. The reason why semaglutide can be provided per OS is the developed research technique of the absorption enhancer sodium N-(8-[2-hydroxybenzoyl] amino) caprylate. It can help semaglutide to be absorbed in the gastric mucosa.

For actual effect of semaglutide, once-daily oral intake and once-week injection were compared [13]. Across several PIONEER programs, oral semaglutide 14 mg had reduced HbA_{1c} by 1.0-1.4%, which was significantly more than empagliflozin or sitagliptin, with similar extent by liraglutide. Both administrations did not increase hypoglycemia and both improved various items of Health-related Quality of Life (HRQOL). Consequently, semaglutide offers benefits in both routes, and can adapt individual situation suitable for needs and preferences. In PIONEER 4 study, phase 3a trials were executed for the comparison with oral semaglutide, subcutaneous liraglutide and placebo [6]. The subjects were 711 T2DM cases from 12 countries with HbA_{1c} 7.0-9.5%. Cases were randomly assigned to 3 groups, which are semaglutide, liraglutide and placebo as 285, 284 and 142 based on certain ratio of the protocol as 2:2:1. The results of these groups showed that HbA_{1c} change was -1.2%, -1.1%, -0.2%, respectively, without significant difference in former two groups. Further, weight reduction was found for 4.4kg vs 3.1kg in semaglutide group vs liraglutide group associated with significant difference.

Successively, clinical effect and safety of semaglutide was studied for PIONEER 9 and 10 trials [14]. The comparison was conducted among oral semaglutide (3, 7, 14mg daily), subcutaneous liraglutide (0.9mg once-daily) and subcutaneous dulaglutide (0.75 mg, once-weekly). The trials were continued for 1 year and among them, 701 cases were included (n=243 in PIONEER 9 and n=458 in PIONEER 10). They showed similar results among three groups and between aged ≥65 versus <65 years. However, adverse events tended

to occur more in aged ≥ 65 years group.

From these data, semaglutide has been rather highly evaluated for its several beneficial aspects as one of GLP-1Ras. For the route of the administration method, it is available for subcutaneous injection and also for oral form. It has medical application for T2DM and obesity for expecting significant weight reduction. In addition, semaglutide can be given safely to elder cases with hepatic and renal dysfunction, without decreasing the amount of the dosis [15]. It can be tolerated enough for no hypoglycemia risk by monotherapy, but it shows some gastrointestinal adverse effects. Thus, semaglutide seems to be prescribed more for its clinical usefulness. Furthermore, GLP-Ras have been known to show several beneficial effects for atherosclerotic cardiovascular disease (ASCVD) and chronic kidney disease (CKD) [16]. These positive effects are not related to improving glucose control. Moreover, GLP-1Ras may improve the influence of risk factors including blood pressure, blood glucose and excessive weight. In the case of CKD or diabetic kidney disease (DKD) with decreased renal function, dose reduction of GLP-Ras has been not required.

For recent report, cost-effectiveness was compared for oral semaglutide+metformin vs empagliflozin+metformin. The subjects were uncontrolled T2DM patients with metformin alone [17]. As a result, price/day was 25.53 vs 11.40 by Danish Krone (DKK), respectively. By calculation on quality-adjusted life-years (QALYs), the comparisons were 99 vs 86 thousand DKK in 5 years, and 447 vs 387 thousand DKK for lifetime.

Conflict of Interest

The author has read and approved the final version of the manuscript. The author has no conflicts of interest to declare.

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