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PUBTEXTO

Effective oral formulation of semaglutide (Rybelsus) for diabetes and obesity due to absorption enhancer development

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Abstract

Glucagon-Like Peptide 1 receptor agonist (GLP-1RA) have been recently effective for diabetes. Among them, subcutaneous injection and oral form of semaglutide (Rybelsus) are in focus, in which the latter has been examined in the Peptide InnOvatioN for Early diabEtes tReatment (PIONEER) studies. Rybelsus could been invented for absorption enhancer sodium N-(8-[2-hydroxybenzoyl] amino) caprylate, due to 30-year process of innovation by Novo Nordisk. It shows clinical effects for diabetes and obesity. For PIONEER 9 and 10 trials, efficacy and safety were shown for 3, 7 or 14 mg of Rybelsus equivalent to subcutaneous liraglutide and subcutaneous dulaglutide for 52 weeks.

Keywords: semaglutide; Rybelsus; Peptide InnOvatioN for Early diabEtes tReatment (PIONEER); absorption enhancer sodium N-(8-[2-hydroxybenzoyl] amino) caprylate; Novo Nordisk

Commentary

Diabetes mellitus and obesity have been more prevalent worldwide. American Diabetes Association (ADA) presented latest Standards of Medical Care in Diabetes on Jan 1, 2022, which becomes standard guideline for clinical practice and research [1]. For pharmacological treatment, recent topic includes Glucagon-Like Peptide 1 receptor agonist (GLP-1RA) for diabetes [2]. GLP-1RA has several beneficial effects compared to other antidiabetic agents [3]. Authors and collaborators have continued diabetic practice associated with the treatment of GLP-1Ra and low carbohydrate diet (LCD) for years [4].

Several kinds of GLP-1RAs have been used for type 2 diabetes mellitus (T2DM) [5]. Each agent has different characteristics of molecular weight and effect duration. Some differences were observed concerning administration method and combined situation. These agents are divided into some categories in the following. They are i) exenatide injected twice daily subcutaneously, ii) lixisenatide and liraglutide injected once daily subcutaneously, iii) exenatide, duraglutide and semaglutide subcutaneously injected once weekly and iv) oral form of semaglutide, which has been examined in the Peptide InnOvatioN for Early diabEtes tReatment (PIONEER) studies.

Systematic review of semaglutide was observed for 11 RCTs of 9890 cases [6]. The results showed decreased HbA1c 0.89% and weight 2.99kg, and superiority of HbA1c and weight as -0.35% and -1.48kg, compared with sitagliptin, empagliflozin and liraglutide. Further, it showed cardiovascular mortality (Odds Ratio, OR 0.55), all-cause mortality (OR 0.58), and the neutral efficacy for stroke, myocardial infarction, diabetic retinopathy and hypoglycemia. From 7 cardiovascular outcome trials (CVOTs) with 56004 patients, semaglutide showed less cardiovascular death than dulaglutide (OR 0.46), exenatide (OR 0.47), lixisenatide (OR 0.43) and albiglutide (OR 0.45) [7].

For clinical effect of semaglutide, phase 3 clinical trial showed weight reduction 1kg by 7mg and 2.2kg by 14mg [8]. A study included multi-centers of 16 countries in Asia, Europe and United States [9]. Subjects were 1961 obese adults with BMI >30 kg/m2. Their average BMI was 38 and weight was 104kg. The results of 68-week showed 14.9% (15.3 kg) weight loss in semaglutide group, while control group showed 2.6kg loss, indicating remarkable efficacy.

Latest reports on 2022 for weight reduction are found. Double-blind trial included semaglutide 2.4mg once-weekly group and placebo group. Subjects were 1961 obesity adults without DM, and observed 68 weeks [9]. Results showed weight reduction for semaglutide vs placebo was -14.9% vs -2.4%, respectively. Weight reduction prevalence at 68 weeks (5%<, 10%<, 15%<) were 86.4% vs 31.5%, 69.1% vs 12.0%, 50.5% vs 4.9%, respectively. For actual weight analysis, weight reduction was -15.3kg vs -2.6kg, respectively. Common adverse events with semaglutide were nausea and diarrhea, which were mild degree and transient and subsided with time. A meta-analysis was conducted including 4 trials with 3447 cases [10]. There were significant achievements of categorical weight reduction, waist circumference, BMI, as well as cardiometabolic risk factors and health-related QOL. These results

suggest clinically beneficial effects.

Regarding oral semaglutide (Rybelsus), historical situation and recent topics would be described. Rybelsus has been invented due to 30-year process of innovation. Formerly, Novo Nordisk had tried to develop inhaled type of insulin product, but they ceased to continue the project. Just after this, they announced the researching situation for oral GLP-1 and insulin in 2008 [11]. It was a brave decision and step. Scientists in the research team were faced two problems. They are i) what kind of drug-delivering technology should be used, and ii) how drug molecule should be delivered as active pharmaceutical ingredient (API).

Most of GLP-1Ras have been administered by subcutaneous injection. For oral formulation of semaglutide, absorption enhancer sodium N-(8-[2-hydroxybenzoyl] amino) caprylate has been developed in progressing research, that can facilitate semaglutide absorption through gastric mucosa. From PIONEER 4 trial, decreasing HbA1c would be similar to liraglutide and oral semaglutide showed superior for reducing weight [12]. Consequently, oral semaglutide is effective option with safety and tolerability.

Semaglutide can be available for both of subcutaneous route and oral dosage form. It was approved by US FDA as second line therapy option for improvement of T2DM and for anti-obesity purpose [13]. Further, it would be safe for older patients with renal and/or hepatic disorders demanding no modification of dose [14]. This agent has been well tolerated for no risk of hypoglycemia in monotherapy, but it has some adverse effects of gastrointestinal (GI) tract. Consequently, semaglutide has been rather highly evaluated for multiple benefits.

As to PIONEER 9 and 10 trials for semaglutide, efficacy and safety for Japanese T2DM patients were investigated [15]. They were provided 3, 7 or 14 mg of oral semaglutide, subcutaneous liraglutide and subcutaneous dulaglutide for 52 weeks. As a result, 701 patients showed clinical efficacy and unremarkable adverse events. Consequently, semaglutide was proved to be efficacious for aged <65 and ≥65 years.

From mentioned above, semaglutide has been investigated in some categories. The characteristic topic is possible oral form administration. Several clinical projects include i) PIONEER, ii) SUSTAIN (Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes) and iii) STEP (Semaglutide Treatment Effect in People with Obesity) clinical trial programs. In each project, semaglutide dose was i) oral administration, ii) 1.0mg, once-weekly subcutaneously, and iii) 2.4mg, once-weekly subcutaneously. From these trials, semaglutide revealed similar effect of glucose variability and more weight loss compared with other anti-diabetic agents [16].

The author would like to add some information about actual case and Novo Nordisk. Among various diabetic patients, 59-year-old female has now just started Rybelsus 3mg/day. She showed decrease of HbA1c 1% and weight reduction 3kg for 4 weeks, and is now on 7mg/day from 5 weeks. Regarding Novo Nordisk, successful development of absorption enhancer caprylate is extremely highly-evaluated. Further, the author and other 11 representative Japanese young diabetologists were invited to international workshop in Steno Hospital and Novo Nordisk for 1 week 30 years ago. At that time, we had learned latest diabetology and appreciated much for the opportunity and consideration. It is continuous support of Novo Nordisk that enabled oral form of semaglutide (Rybelsus). In summary, further contribution of semaglutide to patients and society will be expected in the future.

Ethical Considerations

This research study was fundamentally conducted according to the ethical principles on the Declaration of Helsinki. In addition, some comment was from the Ethical Guidelines for Research for Humans, associated with the concept of Good Clinical Practice (GCP). The authors which are related to this manuscript have established an ethical committee. It is in the hospital, which included the president and director of the hospital, physician, nurse, pharmacist, nutritionist and the professional of legal specialty. Discussion was performed for adequate manners, and it decided to show the agreements for current research Protocol. The informed consent and also written style of the agreement document were obtained from the subject.

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