Yumed Text
OPEN ACCESS JOURNALS

Journal of Diabetes, Obesity & Metabolism

Editorial | Vol 5 Iss 1

Novel oral semaglutide (Rybelsus) with life-changing beneficial effects for diabetic patients

Hiroshi Bando[1,2*]

[1]Medical Research / Tokushima University, Tokushima, Japan

[2]Japan Low Carbohydrate Diet Promotion Association (JLCDPA), Kyoto, Japan

[*]**Corresponding author:** Bando H, Medical Research / Tokushima University, Tokushima, Nakashowa 1-61, Tokushima 770-0943 Japan; Tel: +81-90-3187-2485; E-mail: pianomed@bronze.ocn.ne.jp

Received: April 03, 2022; **Accepted:** April 17, 2022; **Published:** April 24, 2022

Abstract

As one of the Glucagon-like peptide 1 receptor agonists (GLP-1 RAs), oral semaglutide (Rybelsus) become first ingestible agent by absorption enhancer sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC). It was clinically investigated by Peptide InnOvatioN for Early diabEtes tReatment (PIONEER) trials. Pharmacologically, blood concentration of semaglutide is kept higher when fasting time period after intake becomes longer. It is provided for increasing doses of 3 mg, 7 mg, 14 mg in every month. Rybelsus showed higher ratio of adverse effects (AEs), which include gastrointestinal dysfunction and headache. This agent is a novel delivery of therapeutic peptide and become life-changing beneficial agents for diabetic patients.

Keywords: ***Glucagon-like peptide 1 receptor agonists (GLP-1 RAs); Oral semaglutide (Rybelsus); Sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC); Peptide Innovation for early diabetes treatment (PIONEER), Adverse effects (AEs)***

Diabetes has been widely increasing across the world. In 2021, 537 million people are living with diabetes according to International Diabetes Federation (IDF) [1]. It is supposed to be increased to 643 million by 2030 and 783 million by 2045. Especially, 3 in 4 adults are diabetic in low- and middle-income developing countries. For useful reference for diabetic practice, American Diabetes Association (ADA) has announced the standard guideline for diabetes in Jan 2022 [2]. In the light of pharmacological therapy for diabetes, several useful anti-diabetic agents have been reported [3]. Glucagon-Like Peptide 1 receptor agonists (GLP-1RAs) show beneficial effects for several axis organs [4].

Among GLP-1RAs, semaglutide has been the first agent available in the oral formulation for patient with type 2 diabetes (T2D). Oral semaglutide (Rybelsus) was developed by the application of an absorption enhancer, that is sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC). Rybelsus has been administered as three increasing doses as 3 mg, 7 mg, and 14

Citation: Bando H. Novel oral semaglutide (Rybelsus) with life-changing beneficial effects for diabetic patients. J Diab Obes Metab. 2022;5(1):e108.

mg for each month [5]). Several trials were performed for Peptide InnOvatioN for Early diabEtes tReatment (PIONEER) programs [6]. From the results of PIONEER trials, oral semaglutide has been approved and used for T2D in Europe, North America and Japan [1,5]. Clinical manifestation and characteristics for T2D show some differences in East Asia compared with those who in Europe and North America [7]. T2D patients in Asia tends to be developed at lower BMI compared to those in Western countries [1,8]. Moreover, early stage T2D in Asians shows decreased beta-cell function than Caucasians [9].

PIONEER trials have been performed in some countries. Regarding PIONEER 1, monotherapy of oral semaglutide was compared with placebo in T2D [10]. PIONEER 3 was conducted for additional oral semaglutide vs sitaglipitin [11]. In PIONEER 8, compared study was conducted for metformin and insulin [12]. PIONEER 9 has focused in effect, safety and dose-response aspects [13]. For PIONEER 10, clinical efficacy was compared with dulaglutide [14]. As a result, significant HbA1c reduction was observed at 14 mg of Rybelsus, and weight reduction was found at 7 mg and 14 mg in comparison with those of dulaglutide (0.75 mg/week). For both studies, Rybelsus showed high tolerability associated with safety profile, which were similar to other GLP-1Ras [13,14]. Successively, subgroup investigation was found in PIONEER 9 and 10 [15].

Concerning diabetic clinical practice, authors and collaborators have treated a T2D patient with Rybelsus. The case was 51-year-old male showing HbA1c 8.5% and weight 96 kg before treatment. Increasing doses of Rybelsus as 3, 7, 14 mg/day were provided [16]). As a result, significant improvement was found after treatment for 3 months as 7.1% and 91 kg. This seemed to be from his lifestyle with no breakfast and more than 3 hours of fasting after Rybelsus intake with water in early morning. From these situation, longer time period of post-med may contribute higher efficacy of Rybelsus for blood glucose control and weight reduction.

According to a pharmacokinetics report, blood concentration of Rybelsus was examined for different condition [17]. The protocol included fasting time period after taking Rybelsus for 15-120 min. When fasting time was 30 min as the standard level, the results showed 14.6 nmol/L (2 hrs) and 12.3 nmol/L (24 hrs). When it was 120 min, they showed 28.0 nmol/L (2 hrs) and 22.5 nmol/L (24 hrs). In the light of calculated ratios, fasting-30 min showed 1.0, fasting- 60 min showed 1.56 (4 hrs) and 1.48 (24 hrs), fasting-120 min showed 1.83 (4 hrs) and 1.83 (24 hrs) [11]. Consequently, it was clarified that the blood concentration was elevated when fasting time period was longer [18]. These data show stable and beneficial effects of the combination of semaglutide and SNAC in actual clinical practice [19].

Regarding clinical effect and safety on oral semaglutide for patients with T2D, once-daily Rybelsus for 3 mg, 7 mg and 14 mg were provided and investigated [15]. For clinical studies of PIONEER 9 and 10, patients were 711 cases included as n= 243 and 458, respectively. The former was phase II/IIIa, randomized, placebo- and active-controlled which was held 16 centers in Japan for 1 year [13]. The latter was phase III open-label, parallel-group, active-controlled trial which was held 36 centers in Japan for 1 year [14]. Statistically significant relationship was found between baseline HbA1c and weight reduction amount, when Rybelsus 14 mg vs placebo were compared in PIONEER 9 ($p<0.03$). Baseline HbA1c, BMI and medication have not seemed to influence the frequency of adverse events of Rybelsus. Consequently, baseline HbA1c, baseline body mass index and background medication did not appear to affect the proportions of patients reporting adverse

events (AEs). Consequently, Rybelsus seemed to be effective for diabetic cases associated without unexpected safety findings.

GLP-1Ras have been highly evaluated to show various beneficial efficacy to T2D patients. Oral semaglutide (Rybelsus) has been expected for its usefulness of ingestible agent. However, some AEs were reported, which are a little higher percentage than previous agents. Safety investigation was conducted [20]. From food-effect studies of Rybelsus, 167 AEs were found in 64% of the subjects (n=50). Most frequently AEs included gastrointestinal dysfunction and headache. The former was found in 19%, 50%, 27% of i) fed group, ii) fasting, iii) reference, respectively. The latter was observed for 15%, 38%, 35% of same groups. Among them, almost of them were mild degree for 135 reported events. For successive investigation for dosing conditions, 599 AEs were observed of 85% of the subjects (n=134). Gastrointestinal disorders were most frequent for 61% of the subjects. They felt more associated with longer fasting time periods, which seemed to have higher concentration exposure [21].

In summary, recent approval of oral semaglutide by US FDA and others means the remarkable landmark for the novel delivery of therapeutic peptides [22]. This achievement was performed from significant technical, pharmacological, scientific and clinical innovation for years. From some analysis, this product will reach $5 billion for peak revenues [23]. It will probably become one of the life-changing beneficial agents for many diabetic patients [24].

REFERENCES

1. International Diabetes Federation (IDF). Diabetes around the world in 2021. IDF Diabetes Atlas. Tenth Edition. https://diabetesatlas.org/
2. American Diabetes Association. Introduction: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022;45(Suppl 1):S1-S2.
3. ADA Professional Practice Committee. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022;45(Suppl 1):S125-43.
4. Alfayez OM, Almohammed OA, Alkhezi OS, et al. Indirect comparison of glucagon like peptide-1 receptor agonists regarding cardiovascular safety and mortality in patients with type 2 diabetes mellitus: network meta-analysis. Cardiovasc Diabetol. 2020;19(1):96.
5. European Medicines Agency (EMA) 2020. RYBELSUS summary of product characteristics. Available from: https:// www.ema.europa.eu/en/medicines/human/EPAR/rybelsus. Accessed June 10, 2020.
6. Thethi TK, Pratley R, Meier JJ. Efficacy, safety and cardiovascular outcomes of once-daily oral semaglutide in patients with type 2 diabetes: the PIONEER programme. Diabetes Obes Metab. 2020;22(8):1263-77.
7. Ma RC, Chan JC. Type 2 diabetes in East Asians: similarities and differences with populations in Europe and the United States. Ann N Y Acad Sci. 2013;1281(1):64-91.
8. Yoon KH, Lee JH, Kim JW, et al. Epidemic obesity and type 2 diabetes in Asia. Lancet. 2006;368(9548):1681-8.
9. Yabe D, Seino Y, Fukushima M, et al. β cell dysfunction versus insulin resistance in the pathogenesis of type 2 diabetes in East Asians. Curr Diab Rep. 2015;15(6):602.

10. Aroda VR, Rosenstock J, Terauchi Y, et al. PIONEER 1: Randomized Clinical Trial of the Efficacy and Safety of Oral Semaglutide Monotherapy in Comparison with Placebo in Patients With Type 2 Diabetes. Diabetes Care. 2019;42(9):1724-32.
11. Rosenstock J, Allison D, Birkenfeld AL, et al. Effect of Additional Oral Semaglutide vs Sitagliptin on Glycated Hemoglobin in Adults with Type 2 Diabetes Uncontrolled With Metformin Alone or With Sulfonylurea: The PIONEER 3 Randomized Clinical Trial. JAMA. 2019;321(15):1466-80.
12. Zinman B, Aroda VR, Buse JB, et al. Efficacy, safety, and tolerability of oral semaglutide versus placebo added to insulin with or without metformin in patients with type 2 diabetes: the PIONEER 8 trial. Diabetes Care. 2019;42(12):2262-71.
13. Yamada Y, Katagiri H, Hamamoto Y, et al. Dose-response, efficacy, and safety of oral semaglutide monotherapy in Japanese patients with type 2 diabetes (PIONEER 9): a 52- week, phase 2/3a, randomised, controlled trial. Lancet Diabetes Endocrinol. 2020; 8(5):377-91.
14. Yabe D, Nakamura J, Kaneto H, et al. Safety and efficacy of oral semaglutide versus dulaglutide in Japanese patients with type 2 diabetes (PIONEER 10): an open-label, randomised, active-controlled, phase 3a trial. Lancet Diabetes Endocrinol. 2020;8(5):392-406.
15. Yabe D, Deenadayalan S, Horio H, et al. Efficacy and safety of oral semaglutide in Japanese patients with type 2 diabetes: A subgroup analysis by baseline variables in the PIONEER 9 and PIONEER 10 trials. J Diabetes Investig. 2022:10.1111/jdi.13764. Epub ahead of print.
16. Bando H. Clinical Trials of Novel Perspectives on Semaglutide with Injectable and Oral Formulations. SunText Rev Endocrine Care. 2022;2(1):107.
17. Bækdal TA, Breitschaft A, Donsmark M, et al. Effect of Various Dosing Conditions on the Pharmacokinetics of Oral Semaglutide, a Human Glucagon-Like Peptide-1 Analogue in a Tablet Formulation. Diabetes Ther. 2021;12(7):1915-27.
18. Rodbard HW, Rosenstock J, Canani LH, et al. Oral Semaglutide Versus Empagliflozin in Patients with Type 2 Diabetes Uncontrolled on Metformin: The PIONEER 2 Trial. Diabetes Care. 2019;42(12):2272-81.
19. Rybelsus (Semaglutide). [US Prescribing Information]. Available online: http://www.novo-pi.com/rybelsus.pdf. https://www.novo-pi.com/rybelsus.pdf
20. Mosenzon O, Blicher TM, Rosenlund S, et al. Efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment (PIONEER 5): a placebo-controlled, randomised, phase 3A trial. Lancet Diabetes Endocrinol. 2019;7(7):515-27.
21. Kim HS, Jung CH. Oral Semaglutide, the First Ingestible Glucagon-Like Peptide-1 Receptor Agonist: Could It Be a Magic Bullet for Type 2 Diabetes? Int J Mol Sci. 2021;22(18):9936.
22. Li Y, Zhang W, Zhao R, et al. Advances in oral peptide drug nanoparticles for diabetes mellitus treatment. Bioact Mater. 2022;15:392-408.
23. Lewis AL, McEntee N, Holland J, et al. Development and approval of rybelsus (oral semaglutide): ushering in a new era in peptide delivery. Drug Deliv Transl Res. 2022;12(1):1-6.
24. Bando H. Clinical Trials of Novel Perspectives on Semaglutide with Injectable and Oral Formulations. SunText Rev Endocrine Care. 2022;2(1):107.