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Semaglutide: Untangling the Gordian Knot of Glucose Control

Diabetes is a complex syndrome, with multiple causative factors, complications and confounding situations. Ever widening spectrum of pharmacological evolution is trying to match the complexities in diabetes management with gradual addition of newer class of drugs one after another.

THE GORDIAN KNOT OF GLUCOSE CONTROL

Many conventional therapies, however, like traditional sulfonylureas, create a Gordian knot which is difficult to disentangle. In a unicentric approach to achieve euglycemia, unwanted side effects like hypoglycemia and weight gain often occur.[1] These results of glucose-lowering therapy, which were hitherto considered inevitable, have been addressed in the concepts of the glycemic pentad and the KgA1c paradox. The glycemic pentad suggests that avoidance of hypoglycemia and glycemic variability is as important a therapeutic goal as achievement of normal glucose values.[2] The KgA1c paradox reminds us of the deleterious rise in body weight that is often seen when HbA1c is lowered with conventional diabetes control strategies.[3]

GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS

In recent years, injectable glucagon-like peptide-1 receptor agonists (GLP-1RA) have become accepted as first-line injectable therapy in persons with type 2 diabetes, especially those with/at high risk of atherosclerotic cardiovascular disease (ASCVD) and/or chronic kidney disease (CKD).[4-7] GLP-1RA are a multifaceted class of glucose-lowering drugs, which act at various levels of glucose homeostasis to ensure optimization of glucose levels. The glucose-dependent mechanism of action prevents hypoglycemia, while pharmacological actions on the hypothalamus and gastrointestinal (GI) tract ensure avoidance of weight gain, promote weight loss and prevent the KgA1c paradox from setting into motion.

There still remains, however, a slight reluctance to use injections. This avoidance can lead to clinical inertia, and result in suboptimal control.[8] Semaglutide, a novel GLP-1RA, which was earlier available as a once-weekly subcutaneous injectable, has now been formulated as a once daily oral pill.[9]

UNTANGLING THE PHARMACEUTICAL KNOT

Formulating an oral preparation of semaglutide posed multiple challenges to drug developers.

The oral administration of semaglutide or other GLP-1RAs alone led to negligible bioavailability of 0.01%. Protein and peptides like semaglutide get degraded by proteolytic enzymes and low pH. Furthermore, due to high molecular weight, these are not able to permeate through the GI epithelium leading to low absorption. This leads to the lower absorption and very low bioavailability.

This Gordian knot was opened using a absorption enhancer, SNAC {sodium *N*-(8-[2-hydroxybenzoyl] amino)caprylate}. It is a small fatty acid derivative that promotes absorption across gastric epithelium.

SNAC increases the localized pH around the tablet and protects it from degradation by proteolytic enzymes and acidic pH. It helps in absorption of semaglutide through GI epithelium via transcellular route. The action of SNAC is time- and concentration-dependent and is fully reversible. Bioavailability of semaglutide has been increased by 100 times when formulated along with SNAC.[9]

In various pharmacological studies, dose of SNAC has been studied from 150 to 600 mg and it has been found that 300 mg of SNAC is the optimum dose to get the maximum bioavailability. When co-formulated with 300 mg SNAC, 1% of semaglutide usually absorbed in stomach.[10]

CLINICAL TRIALS

A robust phase 3 clinical trial program, based upon results of extensive pre-clinical and early clinical studies, has been published. This supports the easy and effective use of oral semaglutide in diverse patient populations, as monotherapy or in combination with varied concomitant therapy, to achieve a wide-spectrum of desired clinical endpoints (Table 1).

UNTANGLING THE CLINICAL KNOT

The diabetes care physician faces multiple challenges while managing his or her patients. Ensuring patient acceptance, adherence and persistence, while offering an effective and efficient therapy that can be administered with minimal intrusion in the individual's lifestyle, and avoiding adverse events or complications, is a difficult task. Added to these are the needs to ensure vasculo-metabolic and viscera-metabolic safety, and promote cardiovascular health. All these "tasks" are the equivalent of cleaning the Augean stables.

THE PLACE OF ORAL SEMAGLUTIDE

Oral semaglutide, with its unique pharmaco-clinical properties, seems well-poised to be a game changer in glucose control.

Table 1. Summary of Efficacy Outcome in the PIONEER Clinical Trials[11-19]

Trials (N)	Baseline HbA1c	Time Point	Comparator	% mean reduction in HbA1c				Estimated mean change from baseline SBP (mmHg) (on-treatment period)			
				Semaglutide			Comparator	Semaglutide			Comparator
				3 mg	7 mg	14 mg		3 mg	7 mg	14 mg	
PIONEER 2 (822)	8.1	Week 52	Empa 25 mg			−1.3	−0.9			−5	−4
PIONEER 3 (1,864)	8.1	Week 78	Sita 100 mg	−0.6	−1.0	−1.3	−0.8	−2	−3	−3	−0
PIONEER 7 (504)	8.3	Week 52	Sita 100 mg	−1.3	Flex dosing		−0.8	−4	Flex dosing		−2
PIONEER 10 (458)	8.3	Week 52	Dula 0.75 mg	−0.9	−1.4	−1.7	−1.4	−2	−2	−2	−1
PIONEER 9 (243)	8.2	Week 52	Lira 0.9 mg	−0.9	−1.4	−1.5	−1.2	−1	−1	−2	−1
			Placebo				−0.1				−3
PIONEER 4 (711)	8.0	Week 52	Lira 1.8 mg			−1.2	−1.1			−2	−3
			Placebo				−0.2				0
PIONEER 1 (703)	8.0	Week 26	Placebo	−0.9	−1.2	−1.4	−0.3	−4	−4	−5	−2
PIONEER 5 (324)	8.0	Week 26	Placebo			−1.0	−0.2			−7	0
PIONEER 8 (731)	8.2	Week 52	Placebo	−0.6	−0.9	−1.3	−0.1	−1	−2	−5	0

In India, oral semaglutide is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus as monotherapy when metformin is considered inappropriate due to intolerance or contraindications or in combination with other medicinal products for the treatment of diabetes. Its use is endorsed by expert guidance from professional bodies across the world (Table 2).

POSOLOGY

Based on various pharmacological studies, dosing conditions have been optimized. Oral semaglutide has to be given after overnight fasting (~6 hours) with up to 120 mL water. As food affects the absorption of semaglutide, post-dose fasting of 30 minutes is recommended before eating, drinking or taking any other medications. Oral semaglutide has to be initiated with the lowest dose of 3 mg and a 4-week dose escalation to 7 mg and then to 14 mg (if needed) is recommended to reduce the risk of GI adverse events.[25]

A GAME CHANGER, A LIFE CHANGER

The availability of GLP-1RA in an oral formulation, a peptide in a pill, opens the possibility of untangling the

Table 2. Recent Guidelines on the Use of GLP-1RAs[6,20-24]

Organization	Year	Indication for GLP-1RA	Mention of Semaglutide
ADA	2022	Among individuals with type 2 diabetes who have established ASCVD or indicators of high CV risk, established kidney disease, or heart failure, a SGLT2 inhibitor and/or GLP-1RA with demonstrated CVD benefit.	Yes (Inj. Semaglutide 2.4 OW for obesity management in patients with type 2 diabetes)
ADA-EASD	2020	GLP-1RA or SGLT2 inhibitor in patients with established or high risk of ASCVD independently of baseline HbA1c levels and glycemic targets, but also independently of baseline metformin use.	NA
ESC	2021	In persons with T2DM and ASCVD, the use of a GLP-1RA or SGLT2 inhibitor with proven outcome benefits is recommended to reduce CV and/or cardiorenal outcome.	NA
AACE/ACE	2018	GLP-1RA is recommended as monotherapy in individuals with HbA1c <7.5%. In addition, GLP-1RA is recommended in prediabetic patients if glycemia is not normalized with medications such as metformin and acarbose.	No
NICE	2015	If triple therapy with metformin and two other oral drugs is not effective, not tolerated or contraindicated, consider combination therapy with metformin, a sulfonylurea and a GLP-1 mimetic for adults with type 2 diabetes who: • have a BMI of 35 kg/m^2 or higher (adjust accordingly for people from Black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity or • have a BMI <35 kg/m^2 and: ▸ for whom insulin therapy would have significant occupational implications or ▸ weight loss would benefit other significant obesity-related comorbidities. Only continue GLP-1 mimetic therapy if the person with type 2 diabetes has had a beneficial metabolic response (a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months).	NA
South Asian Task Force	2019	As an adjunct to diet and exercise in adults with T2DM. Recommended as monotherapy in a few countries (e.g., dulaglutide in India). Indicated in adults (liraglutide) with established CVD to reduce the risk of major adverse CV events.	Yes (indicated in adults with T2DM as an adjunct to diet and exercise to improve glycemic control; Lowers fasting and postprandial glucagon concentrations; Delays early postprandial gastric emptying)

ADA = American Diabetes Association; ASCVD = Atherosclerotic cardiovascular disease; CV = Cardiovascular; SGLT2 = Sodium-glucose cotransporter 2; GLP-1RA = Glucagon-like peptide-1 receptor agonists; CVD = Cardiovascular disease; ADA-EASD = American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD); HbA1c =Glycated hemoglobin; ESC = European Society of Cardiology; T2DM = Type 2 diabetes mellitus; AACE-ACE = American Association of Clinical Endocrinology/American College of Endocrinology; NICE = National Institute for Health and Care Excellence; BMI = Body mass index.

glucose Gordian knot, and achieving safe and effective glucose as well as weight control. This baro-glycemic optimization should prove to be a game changer for all stakeholders in diabetes care, and a life changer for those who live with type 2 diabetes.

REFERENCES

1. Larger E. Weight gain and insulin treatment. Diabetes Metab. 2005;31(4 Pt 2):4S51-6.
2. Kalra S, Baruah MP, Sahay R, Kishor K. Pentads and hexads in diabetes care: numbers as targets; numbers as tools. Indian J Endocrinol Metab. 2017;21(6):794-6.
3. Davidson J, Kalra S, Singh V, Fegade M, Singh G, Mane A. Resolving the KgA1c paradox in the management of type 2 diabetes mellitus. Diabetes Metab Syndr. 2017;11 Suppl 1:S159-68.
4. Honigberg MC, Chang LS, McGuire DK, Plutzky J, Aroda VR, Vaduganathan M. Use of glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes and cardiovascular disease: a review. JAMA Cardiol. 2020;5(10):1182-90.
5. Greco EV, Russo G, Giandalia A, Viazzi F, Pontremoli R, De Cosmo S. GLP-1 receptor agonists and kidney protection. Medicina (Kaunas). 2019;55(6):233.
6. Buse JB, Wexler DJ, Tsapas A, Rossing P, Mingrone G, Mathieu C, et al. 2019 Update to: Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2020;43(2):487-93.
7. Lingow SE, Guyton JE. Clinical inertia among health care providers in a public health safety-net clinic in the management of type 2 diabetes. J Am Pharm Assoc (2003). 2020;60(5):734-9.
8. Anderson SL, Beutel TR, Trujillo JM. Oral semaglutide in type 2 diabetes. J Diabetes Complications. 2020;34(4):107520.
9. Buckley ST, Bækdal TA, Vegge A, Maarbjerg SJ, Pyke C, Ahnfelt-Rønne J, et al. Transcellular stomach absorption of a derivatized glucagon-like peptide-1 receptor agonist. Sci Transl Med. 2018;10(467):eaar7047.
10. Granhall C, Donsmark M, Blicher TM, Golor G, Søndergaard FL, Thomsen M, et al. Safety and pharmacokinetics of single and multiple ascending doses of the novel oral human GLP-1 analogue, oral semaglutide, in healthy subjects and subjects with type 2 diabetes. Clin Pharmacokinet. 2019;58(6):781-91.
11. Rodbard HW, Rosenstock J, Canani LH, Deerochanawong C, Gumprecht J, Lindberg SØ, et al; PIONEER 2 Investigators. Oral semaglutide versus empagliflozin in patients with type 2 diabetes uncontrolled on metformin: the PIONEER 2 trial. Diabetes Care. 2019;42(12):2272-81.
12. Rosenstock J, Allison D, Birkenfeld AL, Blicher TM, Deenadayalan S, Jacobsen JB, et al; PIONEER 3 Investigators. 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.
13. Pieber TR, Bode B, Mertens A, Cho YM, Christiansen E, Hertz CL, et al; PIONEER 7 Investigators. Efficacy and safety of oral semaglutide with flexible dose adjustment versus sitagliptin in type 2 diabetes (PIONEER 7): a multicentre, open-label, randomised, phase 3a trial. Lancet Diabetes Endocrinol. 2019;7(7):528-39.
14. Yabe D, Nakamura J, Kaneto H, Deenadayalan S, Navarria A, Gislum M, et al; PIONEER 10 Investigators. 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. Yamada Y, Katagiri H, Hamamoto Y, Deenadayalan S, Navarria A, Nishijima K, et al; PIONEER 9 Investigators. 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.
16. Pratley R, Amod A, Hoff ST, Kadowaki T, Lingvay I, Nauck M, et al. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial. Lancet. 2019;394(10192):39-50.
17. Aroda VR, Rosenstock J, Terauchi Y, Altuntas Y, Lalic NM, Morales Villegas EC, et al; PIONEER 1 Investigators. 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.
18. Mosenzon O, Blicher TM, Rosenlund S, Eriksson JW, Heller S, Hels OH, et al; PIONEER 5 Investigators. 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.
19. Zinman B, Aroda VR, Buse JB, Cariou B, Harris SB, Hoff ST, et al; PIONEER 8 Investigators. 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.
20. American Diabetes Association Professional Practice Committee; American Diabetes Association Professional Practice Committee:, Draznin B, Aroda VR, Bakris G, Benson G, Brown FM, Freeman R, et al. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022;45(Suppl 1):S125-S143.
21. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al; ESC National Cardiac Societies; ESC Scientific Document Group. 2021 ESC Guidelines on

cardiovascular disease prevention in clinical practice. Eur Heart J. 2021;42(34):3227-337.

22. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm – 2018 executive summary. Endocr Pract. 2018;24(1):91-120.
23. NICE. Type 2 diabetes in adults: Management 2015. Available at: https://www.nice.org.uk/guidance/ng28/resources/type-2-diabetes-in-adults-management-pdf-1837338615493. Accessed Jan 24, 2022.
24. Kalra S, Das AK, Sahay RK, Baruah MP, Tiwaskar M, Das S, et al. Consensus recommendations on GLP-1 RA use in the management of type 2 diabetes mellitus: South Asian Task Force. Diabetes Ther. 2019;10(5): 1645-717.
25. Oral semaglutide, US Prescribing information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213051s000lbl.pdf. Accessed on Jan 24, 2022.

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South Korea to Remove COVID Restrictions In Spite of Surge in Cases and Deaths

South Korean was preparing for ending COVID restrictions despite reporting 6,21,328 new daily COVID-19 infections and a record high of 429 deaths in a day.

The Korea Disease Control and Prevention Agency (KDCA) said that the current wave has been stronger than expected and the increase in fresh cases was due to the highly infectious Omicron variant which would infect many but severe health issues would be less. The KDCA further stated that 63% of the country's population had received booster shots and 86.6% were fully vaccinated.

Despite the surge, no sign of rethinking plans to lift COVID restrictions was shown by the government. Use of masks is mandatory in all public indoor and outdoor spaces.

A health ministry official said that no deaths were reported among people under 60 who had received a booster shot in the analysis of around 1,41,000 Omicron cases reported in the country over the past year and hence, COVID could be treated like the seasonal flu. (*Reuters, March 17, 2022*)

Immune Status of Older Adults Key Indicator of Severity of a BA.2 Wave in the US

More than 28 million seniors are at risk of severe illness with the new version 'BA.2' of the Omicron coronavirus variant in the United States because of either being partially vaccinated, being unvaccinated or because more than 5 months have passed since their second or third vaccine dose. The CDC data shows that about 15 million older Americans missed their third dose.

An analysis by the UK Health Security Agency revealed that the BA.2 subvariant of Omicron was about 80% more contagious than BA.1, which affected the US last winter. Number of cases and hospitalizations was again surging in the UK and several other European countries due the predominance of the BA.2 strain. The strain could once again adversely affect the healthcare resources in the US if more people are infected by the strain.

Amid all this, the immune status of adults aged above 65 years will be a major indicator of how future variants will impact the US since the risk of severe outcomes is known to increase with age.

Stephen Kissler, who specializes in infectious disease modeling at Harvard's TH Chan School of Public Health, said that the amount of prior immunity that the older adults have, whether from previous infection or vaccination, has been the best indicator of how severe the cases will be, in terms of hospitalizations and deaths.

Experts are of the view that the BA.2 wave in the US may not be as severe as in Hong Kong, but could be similar to the UK. Therefore, vaccinations and boosters for seniors were essential. (*CNN, March 17, 2022*)

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