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CLINICAL PRACTICE UPDATE IN
ENDOCRINOLOGY & DIABETES

Advancements in Diabetes Therapy: An Evolving Landscape of Oral Agents

MICHAEL A. TSOUKAS MD, FRCPC
Assistant Professor of Medicine, McGill
Clinical Investigator, Hygea Medical Clinic
Montreal, Quebec, Canada

ALEXANDER ABITBOL MDCM, FRCPC
Assistant Medical Director, LMC
Toronto, Ontario, Canada

The treatment of type 2 diabetes (T2D) is an evolving area, with an ever-growing gamut of exciting therapeutic options. The past 15 years have brought a plethora of new oral agents and have changed many prescribers' usual approach when managing their patients. The old ways of starting metformin and a sulphonylurea followed by basal insulin are long gone. Individualized strategies tailored to glycemic targets and favouring cardiorenal benefits, while also minimizing the risk of hypoglycemia and weight gain are now standard of care. In the last decade, DPP-4 inhibitors (DPP4i) have established themselves as the leading second-line oral agent after metformin due to their simplicity and paucity of potential adverse effects. However, when we consider recent clinical trial data, the DPP4i's FDA-mandated cardiovascular (CV) safety studies were relatively disappointing. Powered for neutrality in reducing the risk of major cardiovascular events (MACE), the class achieved its desired safety outcomes but no additional CV benefit over standard diabetes care. Would this data if published today justify our usual predilection for DPP4i after metformin?

The Current Landscape

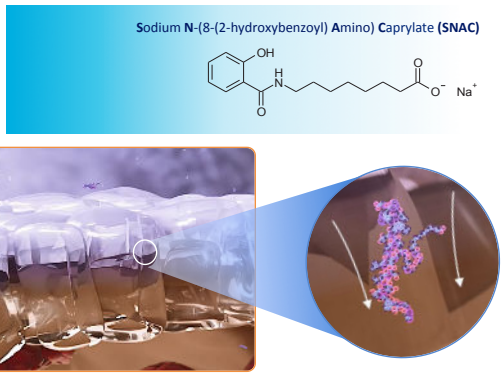
The development and widespread use of the SGLT2 inhibitors (SGLT2i) is supported by additional benefits like MACE prevention, hospitalization for heart failure reduction, and renal protection. Favourable metabolic reductions in glycemia, body weight and blood pressure are also apparent. The risk of adverse effects has led many to overlook the class, but this can be mitigated through proper counselling and shared-care decision making. It is thus logical to consider these agents in combination with metformin early on. In fact, several society guidelines, including the European Cardiovascular Society and the American Association of Clinical Endocrinologists, now boldly recommend starting an SGLT2i prior to metformin, as monotherapy in a select cohort of patients that may benefit from non-glycemic benefits; like heart failure reduction. Injectable GLP-1 receptor agonists (GLP-1RA) also have proven CV benefit and may also soon see recommendations along this same treatment paradigm.

ORAL SEMAGLUTIDE IS A NOVEL AGENT FOR THE TREATMENT OF T2D, AND THE FIRST AND ONLY GLP-1RA AVAILABLE ORALLY.

Oral Semaglutide: A Novel Mode of Action

The "newest kid on the block" is oral semaglutide (Rybelsus®), which was approved in Canada on March 30, 2020. Oral semaglutide is a novel agent for the treatment of T2D, and the first and only GLP-1RA available orally. GLP-1RA enhance the insulin

ABSORPTION OF ORAL SEMAGLUTIDE



response of pancreatic beta cells to elevations in blood glucose, and also suppress hepatic glucagon secretion. Additionally, GLP-1RA promote satiety and decrease gastric emptying. Similar to other GLP-1RA, oral semaglutide has already demonstrated a significant dose-dependent glucose lowering effect, body weight reduction, and an overall low rate of hypoglycaemic events. Its once-daily oral formulation may allay concerns about injections among some patients and clinicians.

Semaglutide is a peptide that is easily digested in the GI tract. To prevent its degradation, an absorption enhancer SNAC [Sodium N-(8-(2-hydroxybenzoyl) Amino) Caprylate] was developed. This small fatty acid derivative promotes absorption of semaglutide across the gastric epithelium. SNAC increases the pH locally, leading to greater solubility, and protection of semaglutide from proteolytic degradation. Oral semaglutide is co-formulated with 300 mg of SNAC to allow its absorption in the stomach. Three daily doses of oral semaglutide are available, which can be uptitrated depending on tolerability: 3 mg, 7 mg and 14 mg. No dose adjustment is recommended based on age, sex, race, ethnicity, upper gastrointestinal disease, or hepatic, and renal impairment.

OVER 20% MORE PARTICIPANTS TREATED WITH SEMAGLUTIDE ACHIEVED A TARGET HBA1C GOAL OF < 7% COMPARED TO EMPAGLIFLOZIN.

As per the product monograph, oral semaglutide should be ingested on an empty stomach at least 30 minutes before the first food, beverage, or other oral medications of the day, with no more than "half glass of water" (120 mL), and then to wait 30 minutes thereafter before ingesting anything else orally. In phase 2 studies, the factors that decreased semaglutide absorption included eating food prior to dosing, ingestion of more than the recommended amount of water, and eating immediately after dosing. Interestingly, only ~1% of semaglutide is absorbed, and the rest is degraded in the GI tract.

The PIONEER studies

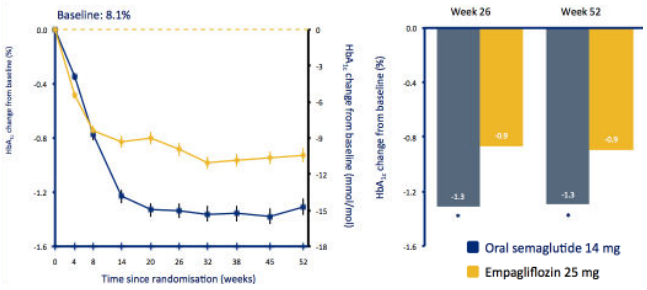
Once oral semaglutide is absorbed, its pharmacodynamic properties and metabolic effects are similar to injectable semaglutide.

PIONEER is oral semaglutide's phase 3 clinical trial program. Oral semaglutide demonstrated significant HbA1c and weight reductions in PIONEER-1. Specifically, the 3 mg, 7 mg and 14 mg doses, decreased HbA1c by 0.9%, 1.2%, and 1.4%, respectively compared with placebo. Body weight decreased by 3.7 kg with semaglutide 14mg daily compared to 1.4 kg in the placebo group.

More relevant to diabetes practitioners today are comparative studies of oral semaglutide with other commonly used oral agents. PIONEER-2 demonstrated superior HbA1c reduction over 52 weeks with semaglutide 14 mg (-1.3%) compared with empagliflozin (Jardiance™) 25 mg (-0.9%). Over 20% more participants treated with semaglutide achieved a target HbA1c goal of < 7% compared to empagliflozin. Weight change was not significantly different between both groups.

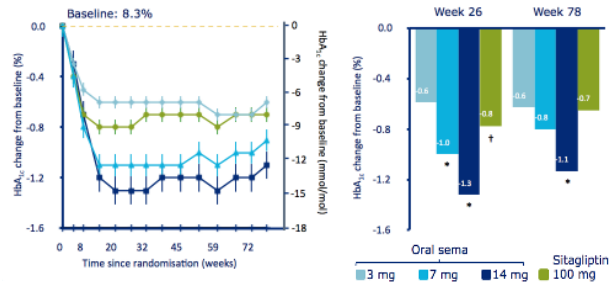
When compared with the most commonly used DPP-4i, sitagliptin (Januvia®), the highest dose of oral semaglutide demonstrated greater HbA1c

PIONEER 2: REDUCTION IN HbA_{1C}
CHANGE FROM BASELINE TO WEEKS 26 AND 52

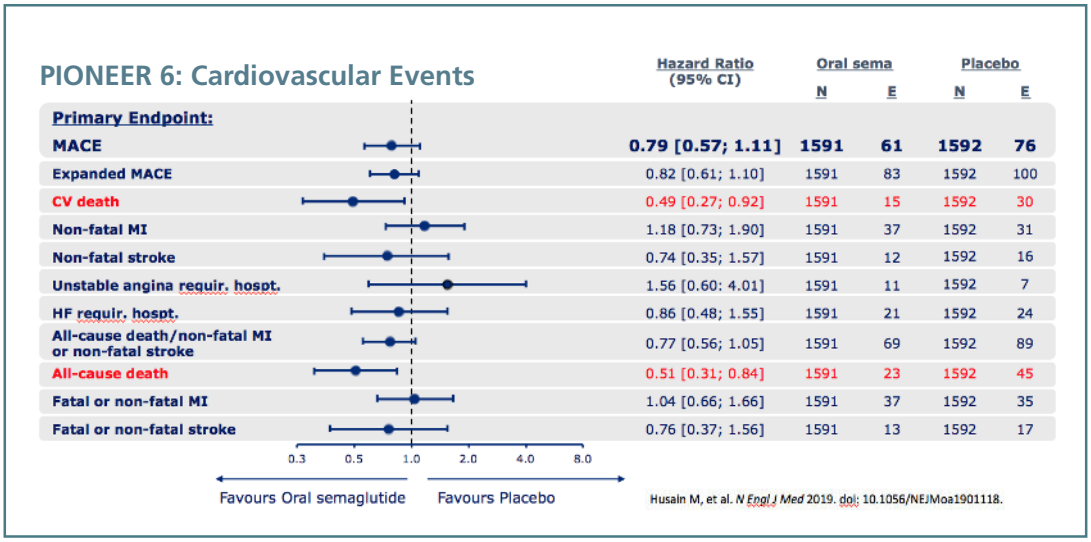


Montanya E, et al. Oral presentation 54-OR. ADA 79th Annual Scientific Sessions 2019.

PIONEER 3: REDUCTION IN HbA_{1C}
CHANGE FROM BASELINE TO WEEKS 26 AND 78



Rosenstock J et al. *JAMA* 2019;321:1–15.



reduction in PIONEER-3. This 78-week trial demonstrated reductions in HbA1c of 0.6%, 0.8%, and 1.1% for doses of 3 mg, 7 mg, and 14 mg of semaglutide, respectively, compared with a reduction of 0.8% for sitagliptin 100 mg daily. Weight loss was significantly greater with all doses of semaglutide compared to sitagliptin.

PIONEER-4 revealed that oral semaglutide was noninferior in reducing HbA1C compared to injectable liraglutide (Victoza®), with significantly greater reductions in body weight observed favouring oral semaglutide. The safety and efficacy of oral semaglutide was evaluated in PIONEER-5, a 26-week clinical study that included patients with moderate renal impairment (eGFR 30 to 59 mL/min/1.73m2), and no overall differences in safety were observed. The 52-week PIONEER-8 trial showed greater HbA1c and body weight reductions for all 3 doses of semaglutide compared to placebo in patients already treated with basal insulin. Using semaglutide also allowed participants to significantly reduce their average daily insulin dose.

Cardiovascular safety

PIONEER-6 is a relatively small size and short duration CV outcome trial, consisting of 3183 participants randomized to oral semaglutide or placebo over a median follow-up of 16 months. Oral semaglutide confirmed CV safety in a high-risk group of participants with a non-significant 21% reduction in the 3-point composite MACE outcome (nonfatal myocardial infarction, nonfatal stroke and CV death) compared with placebo. Significant reductions in the risk of CV death (-51%) and all-cause death (-49%) were also observed. Since the primary endpoint (MACE) was not significantly reduced, these exciting findings are currently considered hypothesis-generating. The ongoing SOUL trial may reveal additional cardiovascular and renal benefits for oral semaglutide. This CV outcome trial has both a larger and more heterogenous population of 9642 participants, and a longer duration of up to 5 years.

Key Takeaways

The novel concept of using combination therapy, even triple therapy (metformin + SGLT2i + GLP-1RA), is supported by the progressive nature of T2D, outcome-driven care (rather than glycemia-driven), and further reinforced by recent statements from both the ADA and EASD. Since the pathogenesis of T2D is complex and involves multiple metabolic defects, use of combination therapy with different classes of antihyperglycemic agents has the potential for an additive reduction in HbA1c, the advantage of preventing adaptive bodily mechanisms that reduce medication effectiveness over time, and the potential for limiting adverse effects often observed with escalations in medication doses.

ORAL SEMAGLUTIDE PROVIDES A ROBUST HBA1C REDUCTION THAT ARGUABLY CAN BE CONSIDERED AS THE GREATEST FOR ALL ORAL AGENTS INDICATED FOR T2D.

Oral semaglutide provides a robust HbA1c reduction that arguably can be considered as the greatest for all oral agents indicated for T2D. Weight reduction, tolerability, and safety profiles have, thus far, been consistent with prior injectable GLP-1RA studies. The most common adverse effect remains mild to moderate nausea.

One potential limitation for oral semaglutide use early on is the very specific administration instructions to maximize absorption. Also, injectable semaglutide has public payor approval in several Canadian provinces, so a relatively higher cost and lack of reimbursement initially for the oral formulation may be the most barrier to access for our patients.

Prescriptions for the GLP-1RA class as a whole is predicted to grow as a result of earlier initiation of oral GLP-1RA therapy, since injectable therapy is often reserved for later on in the disease course. Semaglutide is also gaining the attention from many more healthcare providers today due to compelling efficacy, weight reduction, safety, a minimal risk of hypoglycemia, and potentially CV benefit.

LMC Diabetes & Endocrinology

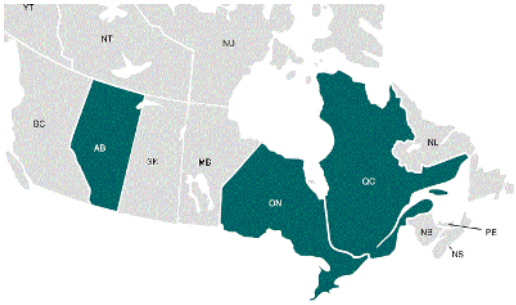
LMC, Canada's largest Specialist Care Provider in Diabetes & Endocrinology is here to support you and your patients during COVID-19

Helpful Guidance for our Patients Living with Diabetes:

- COVID-19 can cause more severe symptoms and complications, including death in some people living with diabetes, the elderly, and those with other chronic conditions such as heart disease & lung disease.
- If diabetes is well-managed, the risk of getting severely ill from COVID-19 is about the same as the general population.
- Remind your patients to NOT stop taking their blood pressure medication, as there is no confirmed scientific link between ACEi or ARB use and the risk of COVID-19 infection or its complications.
- Review COVID-19 & Diabetes resources for Primary Care Physicians and Patients at **lmc.ca/covid19resources/**

LMC Virtual Care Referrals

Our team of Endocrinologists, CDE Nurses, Dietitians and Pharmacists are now offering a wide range of virtual care options to support your patients, including specialist consultations, individualized and group workshops, MedChecks, and more. Virtual capabilities have enabled us to extend the reach of our care to any patient in the 3 provinces that our clinics are located in (Ontario, Quebec & Alberta). We can transfer patients back to your clinic once the COVID-19 crisis is concluded.



To refer your patient today:
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