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Update on GLP-1 Receptor Agonists: Where do these Agents Fit In?

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With a rising incidence of type 2 diabetes (T2D) worldwide and the recognition of the progressive nature of the disease, the need for effective therapies is of utmost importance. Over the past several years, many new medications have emerged for the treatment of T2D, including the glucagon-like peptide-1 receptor agonist (GLP-1 RA) class of medications. These agents increase insulin secretion and decrease glucagon secretion in a glucose-dependent manner, in addition to delaying gastric emptying, decreasing appetite and increasing satiety through their effects on the central nervous system.

Brief History

The first GLP-1 RA used to treat T2D was exenatide (Byetta®), and was approved in 2005. Since then, more GLP-1 RA have emerged, including liraglutide (Victoza®) in 2010, dulaglutide (Trulicity®) in 2016, exenatide extended-release (ER) (Bydureon®) in 2016, lixisenatide (Adlyxine®) in 2017, subcutaneous semaglutide (Ozempic®) in 2018 and, most recently, oral semaglutide (Rybelsus®) in 2020. It is also worth noting that in 2018, two GLP-1 RA have also become available in a fixed-ratio combination (FRC) with basal insulin: insulin glargine/lixisenatide (Soliqua®) and insulin degludec/liraglutide (Xultophy®).

Dosing and Administration

In the interests of practicality, this article will focus on the more commonly used GLP-1 RA: namely, dulaglutide, liraglutide, subcutaneous semaglutide and oral semaglutide. Information on their dosing and administration is summarized in Table 1.

Table 1. Dosing and administration of GLP-1 RA

	Dulaglutide (Trulicity®)	Liraglutide (Victoza®)	Subcutaneous Semaglutide (Ozempic®)	Oral Semaglutide (Rybelsus®)
Picture of injectable device				N/A
Dosing schedule	Weekly	Daily	Weekly	Daily
Initial dose	0.75 mg s.c. weekly	0.6 mg s.c. daily	0.25 mg s.c. weekly	3 mg p.o. daily
Maintenance dose	↑ to 1.5 mg s.c. weekly, if required	↑ to 1.2 mg s.c. daily after 1 week May ↑ to 1.8 mg s.c. daily, if required	↑ to 0.5 mg s.c. weekly after 4 weeks May ↑ to 1 mg s.c. weekly after 4 weeks, if required	↑ to 7 mg p.o. daily after 30 days May ↑ to 14 mg p.o. daily after 30 days at 7 mg p.o. daily

Oral Semaglutide: Now Available as a Once-Daily Tablet

Up until relatively recently, administering a GLP-1 RA orally was not feasible due to its rapid degradation in the stomach by endopeptidases as well as low gastric pH. However, oral semaglutide was made possible via coformulation with the absorption enhancement molecule SNAC (sodium N-(8-(2-hydroxybenzoyl) amino caprylate. SNAC helps to mitigate the proteolytic degradation of semaglutide, in addition to increasing the local gastric pH surrounding the molecule, thereby facilitating its absorption across the gastric mucosa.[1] Notwithstanding SNAC, bioavailability is still quite low such that daily administration is necessary to achieve stable pharmacokinetics.

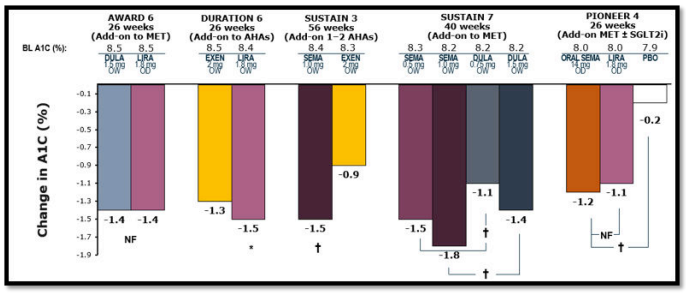
In order to maximize bioavailability, oral semaglutide must be taken upon waking on an empty stomach with a sip (no more than ½ cup) of water. No food, drink or other oral medications should be administered for at least 30 minutes thereafter so as not to interfere with the absorption (and resultant benefit) of semaglutide.

Efficacy

All GLP-RA are effective in lowering A1C, generally on the order of 0.9-1.8%. Several head-to-head trials have been undertaken amongst the various GLP-1 RA (Figure 1).

Subcutaneous semaglutide demonstrated superior A1C reductions versus exenatide ER and dulaglutide (1.5-1.8% with semaglutide vs. 0.9-1.4% with its comparators). Oral semaglutide achieved similar A1C reductions compared with liraglutide (1.2% with oral semaglutide vs. 1.1% with liraglutide).

Figure 1: Changes in A1C observed in head-to-head GLP-1 RA clinical trials



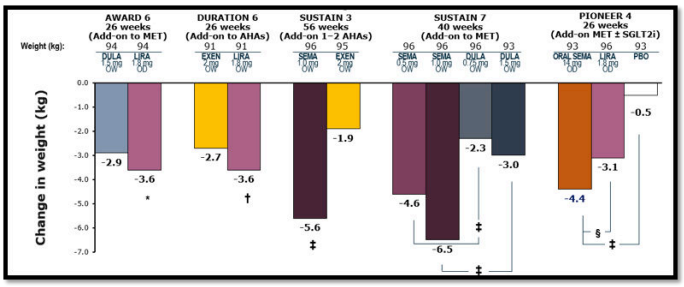
Oral semaglutide was also compared head-to-head with empagliflozin and sitagliptin. At a dose of 14 mg, it lowered A1C by 1.3% in both the PIONEER 2 and PIONEER 3 trials, which was significantly greater than that observed with sitagliptin (0.8%) and empagliflozin (0.9%). [2,3]

Effects on Weight

One of the major advantages of GLP-1 RA, in addition to their A1C lowering efficacy, is their effects on weight. By activating POMC (pro-opiomelanocortin) neurons in the arcuate nucleus of the hypothalamus, GLP-1 RA decrease appetite and increase satiety. Weight loss of 2-6 kg is usually observed. The weight changes attained in the head-to-head trials amongst the various GLP-1 RA are outlined in Figure 2. The greatest magnitude of weight loss has been noted with subcutaneous semaglutide 1.0 mg (ranging from 5.6-6.5 kg), though it is interesting to note that oral semaglutide achieved significantly greater weight loss compared with liraglutide (4.4 kg with oral semaglutide vs. 3.1 kg with liraglutide).

A "start low, go slow" approach to initiating GLP-1 RA is generally the most successful strategy in mitigating against the GI adverse effects.

Figure 2: Changes in body weight observed in head-to-head GLP-1 RA clinical trials



p-values are for statistical superiority unless otherwise noted as non-inferiority (NF). * p=0.011; † p=0.0005; ‡ p<0.0001; § p=0.0003
AHA, antihyperglycemic agent; DULA, dulaglutide; EXEN, exenatide; GLP-1 RA, glucagon-like peptide-1 receptor agonist; LIRA, liraglutide; OD, once daily; OW, once weekly; PBO, placebo; SEMA, semaglutide;
Ahmann AJ, et al. Diabetes Care. 2018;41(2):258-266; Pratley RE, et al. Lancet Diabetes Endocrinol. 2018;6(4):275-286; Pratley R, et al. Lancet. 2019 Jul 6;394(10192):39-50;
Trujillo JM, et al. Ther Adv Endocrinol Metab. 2015;6(1):19-28.

Combination with Basal Insulin

Although basal insulin is effective in lowering fasting glucose levels, achieving target A1C levels may still be challenging for many patients due to postprandial hyperglycemia, which basal insulin does not address. GLP-1 RA are highly effective in reducing postprandial glucose excursions, such that the combination of basal insulin with GLP-1 RA are equally effective as basal-bolus therapy in A1C lowering with the advantages of having a considerably lower risk of hypoglycemia and weight gain.[4] Indeed, for these reasons, Diabetes Canada Clinical Practice Guidelines recommend prioritizing GLP-1 RA over prandial insulin when intensifying beyond basal insulin.[5]

Adverse Effects

The adverse effects of GLP-1 RA tend to be gastrointestinal (GI), and are most commonly observed following treatment initiation and dose escalation. Nausea is observed in up to 25% of patients, while vomiting and diarrhea are observed in up to 13% and 19% of patients, respectively.[6] Constipation, dyspepsia and eructation are other GI adverse effects that may be encountered. For the majority of patients, these adverse effects are transient and mild to moderate in intensity.

A "start low, go slow" approach to initiating GLP-1 RA is generally the most successful strategy in mitigating against the GI adverse effects. Other strategies to minimize the occurrence of GI adverse effects include consuming smaller meal portions, increasing fluid intake, and avoiding fried, fatty or spicy foods.

Cardiovascular Safety

In 2008, the FDA mandated that all new agents for the treatment of diabetes must demonstrate cardiovascular (CV) safety. As such, large CV outcomes trials (CVOT) have been conducted for all GLP-1 RA with the exception of short-acting exenatide, which was approved prior to this requirement. Fortunately, CV safety was established for all GLP-1 RA.

Of note, liraglutide not only reduced major adverse cardiovascular events (MACE) by 13% in the LEADER study, but also decreased CV and all-cause mortality by 22% and 15%, respectively.[7] Subcutaneous semaglutide reduced MACE by 26% in the SUSTAIN-6 trial, though it should be noted that this was a relatively small preapproval cardiovascular safety trial, such that it was not powered to establish superiority.[8] Cardiovascular safety was demonstrated with oral semaglutide in the PIONEER-6 trial, though the much larger SOUL trial (which is anticipated for completion in 2024) is designed to show CV superiority. [9,10]

It is also worth noting that the REWIND trial (CVOT with dulaglutide) was unique in that it demonstrated a 12% reduction in MACE despite the vast majority (69%) of subjects being high-risk primary prevention patients.[11] In contrast, in the other GLP-1 RA CVOT, 81-100% of patients had established cardiovascular disease (CVD).

Where do GLP-1 RA Fit In?

In 2020, Diabetes Canada released an update for the chapter on pharmacologic glycemic management of type 2 diabetes in adults (Figure 3).[12] In essence, based on overwhelming clinical trial evidence, GLP-1 RA and SGLT2 inhibitors are prioritized for patients

GLP-1 RA and SGLT2i are now considered not only glucose-lowering agents, but also agents aimed at CV risk reduction.

with a history of atherosclerotic CVD, chronic kidney disease (CKD), heart failure (HF) or adults over 60 years old with at least 2 CV risk factors. This is the case even if the A1C is at target, which is a paradigm shift. Hence, GLP-1 RA and SGLT2i are now considered not only glucose-lowering agents, but also agents aimed at CV risk reduction.

Otherwise, for patients without the above-mentioned comorbidities whose A1C is above target, GLP-1 RA are one of the many choices that can be used after metformin. Along with SGLT2 inhibitors, they are highlighted as having the advantages of promoting weight loss without increasing the risk of hypoglycemic episodes.

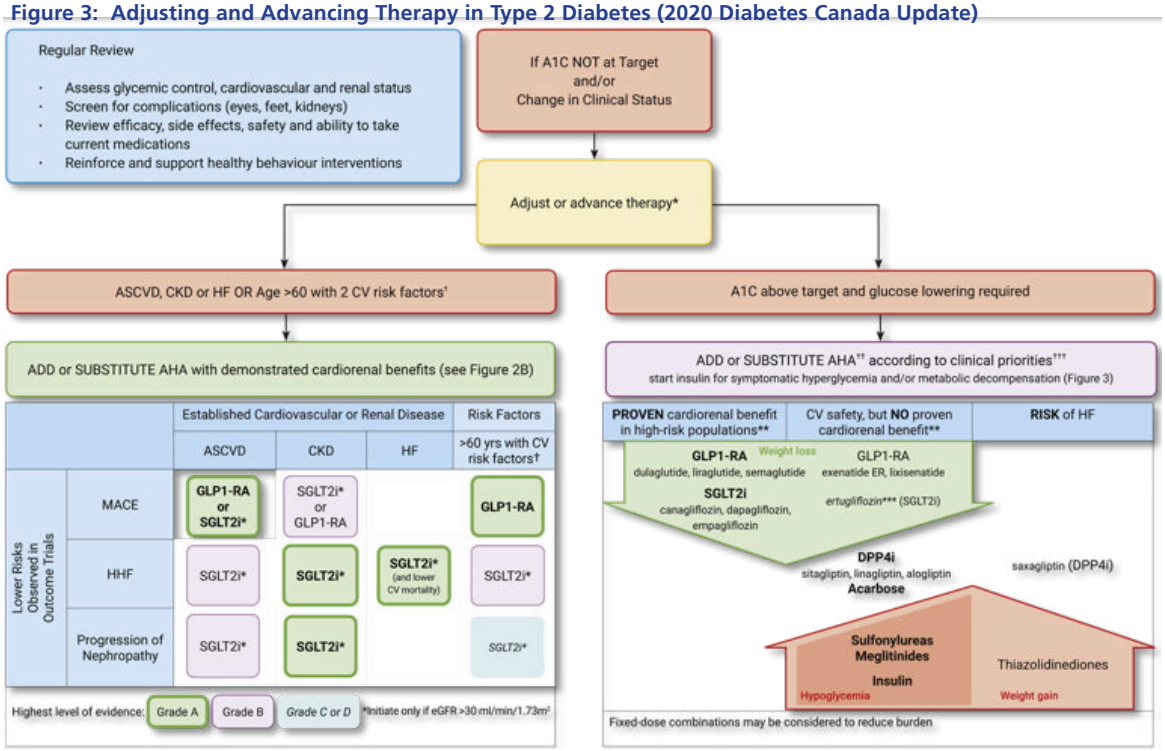
On the other hand, for patients with needle phobia or concerns about their ability to correctly self-administer an injection, an orally available tablet is a welcome alternative. As well, adherence to oral tablets may be improved over injectables in a subset of patients, notwithstanding rather specific daily administration requirements.

Physicians may perceive that some of their patients will be unable to adhere to or have technical difficulty administering an injectable therapy. Furthermore, generally physicians are more uncomfortable prescribing injectable therapies compared to oral ones. In these instances, oral semaglutide may be a more suitable alternative.

For patients taking levothyroxine, which cannot be co-administered with oral semaglutide and has fairly similar administration requirements, the subcutaneous formulation of semaglutide may be more pragmatic.

There was a network meta-analysis that showed no statistically significant difference in efficacy between oral semaglutide 14 mg and subcutaneous semaglutide 1.0 mg, though the latter had numerically greater A1C lowering. It is also noteworthy that weight loss with oral semaglutide was greater than all other GLP-1 RA comparators with the exceptions of subcutaneous semaglutide 0.5 mg and 1.0 mg.

Figure 3: Adjusting and Advancing Therapy in Type 2 Diabetes (2020 Diabetes Canada Update)



Summary

We have a variety of pharmacotherapy options in our toolkit for the treatment of T2D. GLP-1 RA possess many favourable features, including robust A1C lowering and weight loss, no increased risk of hypoglycemia, and CV safety (and even CV benefits for some agents). For those apprehensive about using an injectable therapy, oral semaglutide is a viable alternative. With all the agents at our disposal, we can now better individualize therapy leading to greater benefits for our patients.

Selecting Between Subcutaneous vs. Oral Semaglutide

Both oral and subcutaneous semaglutide have their advantages and disadvantages. When deciding between these two formulations, it is important to have an informed discussion with the patient as this decision is an individualized one (rather than "one-size-fits-all").

When deciding between these two formulations, it is important to have an informed discussion with the patient as this decision is an individualized one (rather than "one-size-fits-all").

Subcutaneous semaglutide, despite being an injectable therapy, only requires once-weekly administration without the stringent administration requirements of its oral counterpart. For these reasons, many patients would in fact find subcutaneous semaglutide easier to adhere to.

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- BMI: 18 – 35 kg/m2
- Medically stable (no major medication changes or new diagnosis 1 month before enrollment)
- Willing to use a smart phone during the study

***Note: Additional eligibility criteria will also apply**

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