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COMMENTARY

Oral Semaglutide: Dosage in Special Situations

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ABSTRACT

Glucagon-like peptide 1 receptor agonists (GLP1RAs) have recently gained momentum after the introduction of semaglutide, the first oral molecule in their class. In a recent article in this journal by Evans et al., a succinct overview of the utility of semaglutide is highlighted in the context of virtual diabetes care. To take this discussion further, this commentary describes the value and positioning of oral semaglutide in common clinical situations. Its insights assist in pragmatic placement of this drug in clinical practice. Special emphasis is laid on the use of oral semaglutide in persons already on injectable GLP-1RA formulations, those experiencing sudden changes in life style pattern due to religious, social, or professional commitments, individuals seeking help for urgent glycemic control, and those who face sudden change in their concomitant medications or comorbidities.

Keywords: GLP1RAs; Obesity; Diabetes care; Ramzan; Semaglutide

Key Summary Points

Glucagon-like peptide 1 receptor agonists (GLP1RAs) have recently gained momentum after the introduction of semaglutide, the first oral molecule in their class.

This manuscript describes the value and positioning of oral semaglutide in common clinical situations. Specific tips on how to prescribe this drug in a large spectrum of people living with type 2 diabetes are mentioned.

The utility of oral semaglutide in those using injectable GLP-1RA formulations, those having sudden changes in their life style pattern due to religious, social, or professional commitments, those seeking help for urgent glycemic control, or those experiencing a sudden change in their concomitant medications or comorbidities is explained.

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INTRODUCTION

Glucagon-like peptide 1 receptor agonists (GLP1RAs) are well accepted for the management of type 2 diabetes [1]. Their impact on weight and vascular tone contributes to cardiovascular safety and is a major benefit associated with this class of drugs [2, 3]. However, their acceptance has been suboptimal, perhaps owing to their injectable nature [4]. Moreover, these drugs were not considered frontline choices by clinical practice guidelines until recently. This, along with the cost, gastrointestinal side effects, risk of pancreatitis, and relative novelty, has precluded their routine use [4]. The availability of oral semaglutide has created new opportunities for the use of GLP1RA in a patient-friendly manner. Evans et al. share a pragmatic approach to the placement of oral semaglutide in clinical practice, and also describe practical tips regarding the posology of the drug [5]. We add to this by highlighting certain other common situations that may require subtle changes in medication counseling. This is a commentary, based on the expert opinion of the authors, and is in accordance with the ethical guidelines for publishing any manuscript. It does not contain any studies with human participants or animals performed by any of the authors.

PERSONS ON DAILY INJECTABLE GLP1RA

Persons on daily injectable GLP1RA (exenatide, liraglutide, lixisenatide) who interchange to oral semaglutide may take their first dose the day after discontinuation of previous therapy. As mentioned by Evans et al., a detailed explanation of the method of drug administration must be shared with the patient. Oral semaglutide usage may be associated with gastrointestinal side effects, but these are usually mild and transient [6].

If this interchange is prompted by lack of tolerability, oral semaglutide should be initiated at 3 mg/day for 1 month, after which the dose can be up-titrated. If the shift is due to lack of efficacy of 10 μg twice daily (BD) exenatide, 20 μg once daily (OD) lixisenatide, or 1.2 mg once daily (OD) liraglutide, one may consider initiating oral semaglutide at 7 mg/day. While some experts propose a 14 mg/day starting dosage for persons on 1.8 mg liraglutide, we suggest a more cautious approach, to minimize potential side effects and ensure patient comfort. These suggestions are based only on expert opinion of the authors and previously published suggestions.

If the switch is requested for reasons of convenience, i.e., to avoid injectable therapy, a 3 mg oral semaglutide dose can be used to substitute for 5 μg BD exenatide, 10 μg OD lixisenatide, or 0.6 mg OD liraglutide. Although the manufacturers do not provide equivalent doses of different GLP-1RAs, these have been proposed previously by other experts [6]. People on a higher dose of these injectables can be directly transitioned to 7 mg oral semaglutide [7].

PERSONS ON ONCE-WEEKLY GLP1RA

People who switch from once-weekly exenatide, dulaglutide, or semaglutide should start oral semaglutide 7 days after their last injection. Similar principles, as detailed above, apply to the choice of dose of initiation. A prescription of oral semaglutide that is started in response to lack of tolerability should begin with 3 mg daily [6]. However, if oral semaglutide is chosen owing to lack of efficacy of current therapy, one may commence with 7 mg/day.

Once-weekly semaglutide has been compared with oral semaglutide, i.e., 0.5 mg once-weekly semaglutide with 7 mg of oral semaglutide [8, 9]. However, the difference in the impact on weight should be explained to the patient.

SHIFT WORKERS

Oral semaglutide is administered in the morning before breakfast. This may be a challenge in shift workers, especially those who work night shifts. In such individuals, the patient may

consider taking oral semaglutide with 6 h fasting and half an hour before the major meal of the day, or before the meal that is preceded by the longest inter-meal gap (6 h or more). As the half-life of oral semaglutide is 7 days, the timing of administration can be changed from day to day, on the basis of shift duty and meal pattern [9, 10].

RAMADAN FASTING

Ramadan fasting is characterized by month-long fasting from dawn to dusk, during which faithful believers abstain from food and water. Oral semaglutide can be taken 30–60 min before the *suhur* (early morning) meal, but this may be inconvenient for many. Another option is to take the drug before the *iftar* (evening) meal, but this will extend the fasting period by a half hour to one hour, and will not be welcome.

Another option is to take oral semaglutide half an hour before midnight snacks, which can be taken before or after Tarawih prayers. Consuming semaglutide tablet with up to half a glass of water, offering the prayer, and then taking a small snack may be an effortless way of taking the drug without intruding into one's lifestyle. It is advisable to always keep a minimum of 6 h of fasting before taking oral semaglutide to achieve the desired bioavailability.

The following key dosing instructions should also be followed during Ramadan fasting.

1. The drug should be taken with minimal water not exceeding 120 ml or 4 oz.
2. The patient should wait 30 min after taking the drug before consuming any food/drink/medication.
3. It is also suggested that, although a patient should wait 30 min before consuming food, the patient ideally eat a snack/food within 30–60 min after taking this drug.
4. It is recommended that tablet semaglutide remain in the blister pack till consumption and not be placed in a pill box.
5. Co-administration of oral semaglutide may have a small impact on certain drugs like metformin, furosemide, rosuvastatin, and thyroxine, and their effect should be monitored from time to time.

SUDDEN CHANGE IN LIFESTYLE/DIET

Oral semaglutide is a safe drug, with minimal risk of hypoglycemia. Hence, if there is a sudden change in lifestyle or dietary pattern, there should be no need to alter the dose of semaglutide. One must counsel the patient, however, to report such developments to the treating physician. It may be necessary to modify the dosage of concomitant sulfonylurea or insulin therapy [9, 10].

SUDDEN CHANGE IN CONCOMITANT THERAPY

People living with diabetes are often treated by multiple health care professionals. It may be possible, for example, that a person on semaglutide is prescribed thyroxine, proton pump inhibitor, or oral bisphosphonate by another physician. It is also conceivable that the person starts a complementary therapy such as high-fiber diet supplements, seeds, or spices in the morning. All these may influence the absorption of oral semaglutide, or may be impacted by it. Patients on semaglutide must be requested, and reminded repeatedly, to inform their treating diabetes care professional if there is any change in concomitant therapy [9–12].

SUDDEN CHANGE IN MEDICAL STATUS

If a person on oral semaglutide experiences sudden change in medical status, an individualized decision should be taken regarding continuation of therapy. Patients who are able to eat and hydrate themselves well, and have stable hepatorenal function, should continue the drug. Those who are unable to eat properly, have vomiting or diarrhea, or are admitted to intensive care will require discontinuation of

GLP1RA, and may benefit from short-term insulin therapy [13].

Such decisions must be based upon a comprehensive assessment of the patient's needs, and should be revised on a regular basis.

NEED FOR URGENCY IN GLUCOSE CONTROL

The prescribing information for oral semaglutide mentions that dose escalation should be done after 1 month. This advice is aimed at minimizing gastrointestinal symptoms and maximizing patient comfort [9, 10].

There may be situations, however, where patients need urgent glucose control, to resolve symptoms, comorbidities, or complications of diabetes. Others may be concerned about their glucose levels, and may ask for early control.

If such people demonstrate good gastrointestinal tolerance to the 3 mg or 7 mg dose of semaglutide, one may consider dose up-titration after 10 or 20 days of therapy. Patients must be counseled about the possibility of transient symptoms, and how to mitigate them.

CONCLUSION

Oral semaglutide is a welcome addition to diabetes therapy. As evidence and experience accumulate, its use will become more effective and efficient. More evidence is needed, however, regarding the impact of oral semaglutide on absorption of alcohol and other drugs and in those with diabetic gastroparesis. This commentary, based on the expert opinion of the authors and suggestions mentioned in other peer-reviewed published papers [14], shares clinical tips on how to use the drug, in a safe and smart manner, in a wider spectrum of people living with type 2 diabetes. This will ensure rational use of this molecule in a safer and more effective method. Diabetes care is a dynamic field, and oral semaglutide counseling will continue to be updated as research and real-world experience evolve.

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