JIM Research Letter

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Switching from subcutaneous to oral semaglutide in type 2 diabetes: A prospective study

Dear Editor,

Semaglutide is a glucagon-like peptide 1 receptor agonist (GLP-1 RA) that leads to significant improvements in weight and HbA1c in patients with type 2 diabetes (T2D) [1, 2]. In 2022 and 2023, the worldwide shortage of subcutaneous semaglutide has limited access to this medication. In this regard, recommendations to mitigate the consequences of the supply shortage of GLP-1 RA, including temporary switching to oral semaglutide in patients receiving subcutaneous semaglutide, have been provided by several organizations. However, there are no studies evaluating the implications of the modification of this treatment. Therefore, we aimed to evaluate the impact of switching from once-weekly subcutaneous semaglutide to once-daily oral semaglutide in patients with T2D in the context of drug shortage.

We conducted a prospective study at the Department of Endocrinology, Virgen de la Victoria University Hospital (Malaga, Spain) including patients with T2D treated with subcutaneous semaglutide 1 mg/week (treatment duration >6 months with this dose), and HbA1c <8%. Participants with HbA1c ≥8% were excluded to avoid treatment interferences, as they were candidates for treatment intensification. Patients with additional criteria for T2D treatment intensification/adjustment or undergoing modifications in the last 6 months were also excluded. From November 2022 to February 2023, in the context of subcutaneous semaglutide shortage, participants switched from subcutaneous semaglutide (1 mg/week) to oral semaglutide (14 mg/day). Clinical and biochemical data were obtained at baseline and 3 months following treatment modification. No changes in glucose-lowering medications (including insulin adjustments) were performed during the study. A paired Student's *t*-test was used for comparisons. The Diabetes Treatment Satisfaction Questionnaire-change version (DTSQc) [3] was used to assess changes in treatment satisfaction. The primary outcome was a change in HbA1c and weight from baseline, together with changes in treatment satisfaction. This study was approved by the Ethics Research Committee of Malaga and was conducted according to the Declaration of Helsinki.

Table 1. *Clinical characteristics of the study population at baseline.*

Age (years, mean ± SD)	58.8 ± 9.7
Sex (*n*, %)	
Male	27 (56.2%)
Female	21 (43.8%)
Duration of diabetes (years, mean ± SD)	11.9 ± 8.5
Use of metformin (*n*, %)	39 (81.3%)
Use of SGLT2i (*n*, %)	32 (66.7%)
Use of other oral glucose-lowering agents (*n*, %)	2 (4.2%)
Insulin therapy (*n*, %)	19 (39.6%)
Hypertension (*n*, %)	31 (64.6%)
Retinopathy (*n*, %)	4 (8.3%)
Neuropathy (*n*, %)	1 (2.1%)
Nephropathy (*n*, %)	6 (12.5%)
Coronary artery disease (*n*, %)	7 (14.6%)
Stroke (*n*, %)	1 (2.1%)
Peripheral artery disease (*n*, %)	1 (2.1%)
Heart failure (*n*, %)	3 (6.3%)
Treatment duration—s.c. semaglutide 1 mg (months, mean ± SD)	19.2 ± 9.9

Abbreviations: s.c., subcutaneous; SD, standard deviation; SGLT2i, sodium–glucose cotransporter 2 inhibitors.

Basal characteristics of the study population are shown in Table 1. In total, 48 patients with T2D were included (7 subjects had been previously excluded due to the need for treatment intensification). Mild adverse gastrointestinal effects were reported in eight participants (six presented nausea and two diarrhea). Of note, four of the aforementioned patients discontinued treatment for this reason (three presenting nausea and one diarrhea) and one patient underwent bariatric surgery before the study's completion and was excluded from the final analyses. The main clinical characteristics

of the participants excluded from the analyses were similar to those who were finally included (Table S1). Therefore, 43 patients were analyzed. Changes in weight and HbA1c were assessed from baseline to 3 months. Notably, no differences in weight (98.6 ± 17.9 vs. 98.4 ± 17.5 kg; $p = 0.619$), body mass index (34.5 ± 5.8 vs. 34.5 ± 5.7 kg/m^2; $p = 0.645$), or HbA1c levels (6.52% ± 0.83% vs. 6.65% ± 1.03%, mean change 0.13%; $p = 0.064$) were observed. DTSQc's scores are shown in Table S2. Overall, treatment satisfaction decreased as compared to baseline. Participants were particularly less satisfied with oral semaglutide for items 4 (convenience), 5 (flexibility), and 8 (satisfaction to continue with present treatment), compared to subcutaneous semaglutide.

In this study, we show that switching from higher doses of once-weekly semaglutide to the once-daily oral formulation of this molecule in patients with T2D did not result in significant changes in weight or HbA1c in the short term. On the other hand, a decrease in treatment satisfaction was observed following this modification.

Despite the fact that some meta-analyses have compared the efficacy of oral semaglutide versus other GLP-1 RA [4, 5], no head-to-head comparisons between the approved higher doses of oral and subcutaneous semaglutide have been performed. In a phase 2, open-label, dose-finding trial exploring the efficacy of doses of 2.5/5/10/20/40 mg of once-daily oral semaglutide, no statistically significant differences were found between doses of 20/40 mg of oral semaglutide and subcutaneous semaglutide (1 mg) [6]. Nevertheless, there is no previous real-world evidence of the effects of switching between the different formulations of this molecule. Although no significant changes in weight or HbA1c were detected after the switch in our study, it should be noted that the p value for HbA1c was close to statistical significance. Indeed, it cannot be ruled out that a statistically significant p value might have been detected with a larger sample size. However, given the observed differences, these changes in HbA1c may be less clinically relevant.

Patient-reported outcomes are increasing in importance in clinical studies. In this regard, oral semaglutide improved treatment satisfaction assessed by the DTSQ in patients with T2D compared to placebo, whereas treatment satisfaction has been reported to be similar to other GLP-1 RA, such as liraglutide [7]. In the REVISE study, a cross-sectional survey of patients with T2D (92.8% taking oral glucose-lowering agents and 26.3% using injectable formulations), participants initially preferred a once-daily oral formulation (76.5%) over a once-weekly injectable (23.5%), although no differences in preferences were detected when detailed information about product-specific administration was provided [8]. However, in light of our results, patients with long-term treatment with subcutaneous semaglutide may prefer this route, due to better convenience and flexibility.

This study has some limitations. First, these findings should be cautiously interpreted due to the limited sample size. Moreover, the effects of switching from subcutaneous to oral semaglutide were assessed in the short term, and results might differ in longer follow-ups, or in patients with different characteristics. On the other hand, this study's main strength lies in its prospective design. Furthermore, to our knowledge, this is the first study that evaluates the impact of subcutaneous-to-oral semaglutide switch in patients with T2D.

In conclusion, in the context of GLP-1 RA shortage, once-daily oral semaglutide (14 mg) might be a useful alternative to once-weekly subcutaneous semaglutide (1 mg) for patients with T2D in the short term. However, patients with previous use of subcutaneous semaglutide may prefer this treatment to the oral formulation.

Author contributions

Conceptualization and study design; data collection; data analysis and interpretation; original draft preparation; manuscript review and editing: José Ignacio Martínez-Montoro. *Conceptualization and study design; data analysis and interpretation; manuscript review and editing*: María José Picón-César. *Data collection; manuscript review and editing*: Marta Generoso-Piñar, Andrea Fernández-Valero, Ángel López-Montalbán, Víctor José Simón-Frapolli, Juan Hernández-Bayo. *Manuscript review and editing*: José Luis Pinzón-Martín. *Conceptualization and study design; supervision*: Francisco J. Tinahones. All authors read and approved the final version of this manuscript. José Ignacio Martínez-Montoro and Francisco J. Tinahones are the guarantors of this study.

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Conflict of interest statement

No potential conflicts of interest relevant to this article were reported.

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Data availability statement

The data that support the findings of this study are available on request from the corresponding author.

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