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Differences in weight loss and safety between the glucagon-like peptide-1 receptor agonists: A non-randomized multicenter study from the titration phase

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ABSTRACT

Introduction: Obesity increases the risk of type 2 diabetes mellitus and cardiovascular disease (CVD). Weight loss (≥5 %) reduces the risk of CVD. Glucagon-like peptide-1 receptor agonists (GLP1 RA) have shown clinically weight loss. Objectives: 1) To assess differences in the efficacy of weight loss and HbA1c; 2) to evaluate the safety and adherence during the titration phase.

Methods: It is a multicenter, prospective, and observational study on GLP1 RA naïve patients. The primary end point was the weight loss (≥5 %). Changes in weight, BMI and HbA1c were also calculated as co-primary endpoints. Secondary endpoints were safety, adherence, and tolerance.

Results: Among 94 subjects, 42.4 % received dulaglutide, 29,3 % subcutaneous semaglutide, 22,8 % oral semaglutide. 45 % female and the mean age was 62. Baseline characteristics were body weight 99.3 kg, BMI 36.7 kg/

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m^2 and Hba1c 8.2 %. Oral semaglutide achieved the highest reduction: 61.1 % of patients achieving ≥ 5 %, subcutaneous semaglutide 45.8 % and dulaglutide 40.6 %. GLP1 RA significantly reduced body weight (−4.95 kg, $p < 0.001$) and BMI (−1.86 kg/m^2, $p < 0.001$), without significant differences between groups. Gastrointestinal disorders were the most frequently reported events (74.5 %). 62 % of patients on dulaglutide, 25 % on oral semaglutide and 22 % on subcutaneous semaglutide.

Conclusions: Oral semaglutide achieved the highest proportion of patients that lost ≥ 5 %. GLP1 RA significantly reduced BMI and HbA1c. Most of the reported adverse events were gastrointestinal disorders and they were reported in a major frequency in the dulaglutide group. Oral semaglutide would be a reasonable switch in case of future shortages.

1. Introduction

1.1. Background

The *International Diabetes Federation Diabetes Atlas* estimates that 510 million people have diabetes around the world in 2021, 91 % of whom have type 2 diabetes mellitus (T2DM) [1]. The presence of diabetes nearly doubles the risk for cardiovascular disease (CVD) [2], and diabetes is also associated with other potentially fatal conditions, including cancer and life-threatening infections [3]. On the other hand, it is estimated that about 2 billion adults present overweight and 600 million have obesity [4]. Obesity increases the risk of T2DM and CVD, in part related to genetic and lifestyle-related causes [5] leading to high health-care costs attributable to obesity related diseases [6]. It is also known that moderate weight loss (5–7 % of body weight) improves the control of blood glucose and reduces the risk of developing CVD [7].

We have currently a hight available number of drugs for the management of T2DM, including oral and injectable drugs. Current guidelines from the *American Diabetes Association* recommend a *glucagon-like peptide-1 receptor agonists* (GLP1 RA) as first line therapy in patients with T2DM and high cardiovascular risk or established CVD. They also recommend starting prior to *insulin* when an injectable drug is necessary and in the overweight population [8]. Several randomized trials with GLP1 RA have showed efficacy by reducing HbA1c and major cardiovascular events (MACE) just as they have also showed clinically weight loss versus placebo but even with active comparators, including other GLP1 RA [9–13]. Consistent with this, two recent meta-analyses have also demonstrated long-term cardiovascular and renal benefits with GLP1 RA [14,15]. However, there is a paucity of clinical trial evidence comparing the efficacy and adverse effects of the different GLP1 RA treatments with each other. In addition, clinical trials often exceed the real-world effectiveness, due in part to lower adherence and discontinuation therapy in real-world, as well as the lack of representativeness among clinical trial participants. Furthermore, GLP1 RA are known to cause gastrointestinal events, and while these effects may reduce after initial use, they have been shown to negatively impact adherence [16].

The use of GLP1 RA in Spain is limited to individuals with T2DM and a body mass index over 30 kg/m2 who cannot achieve their glycaemic control goals. The demand for weekly administration presentations of dulaglutide and semaglutide has recently increased significantly, accounting for 82 % of all aGLP-1 prescriptions. Due to supply chain problems in Europe, the Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) has issued recommendations for the use of these drugs in 2023 [17]. AEMPS recommends prioritizing the use of these treatments for patients with T2DM, avoiding starting new treatments with GLP1RA until the supply issue is resolved. It is also recommended to replace the treatment with one from the same therapeutic group if the drug is unavailable.

1.2. Objectives

For all these reasons, we designed a multicenter, prospective, observational study, aimed to: 1) To assess the initial differences in the efficacy of weight loss and HbA1c reduction between the different GLP1 RA in real world; 2) to evaluate the safety and adherence during the titration phase; and as additional objective, and as a result of a current important issue in the supply chain of these drugs, to select the potential future switches due to the AEMPS restrictions and recommendations.

2. Methods

2.1. Study design

This study is a multicenter, prospective, and observational trial including those patients that started treatment with GLP1 RA in routine clinical practice across 13 primary care pharmacist consultationsthat are part of the Spanish national health system. This primary analysis is enclosed into a larger protocol (*SEVERAL*) already published [18] and registered in *clinicaltrial.gov* (NCT05136287). The protocol was approved by the ethics committee (CEIm) and by the AEMPS in early 2022.

2.2. Setting and population

The participants were recruited from 13 health institutions in Spain from February 2022 to July 2022, and they were followed for 3 months. The inclusion criteria were people over 18 years old with T2DM, BMI > 30 Kg/m^2 and a first GLP1 RA prescription: *semaglutide*, *liraglutide, exenatide, dilaglutide* or *lixisenatide*. Exclusion criteria consisted of the conditions specified in the technical specifications, as well as unwillingness or inability (e.g. physical or cognitive) to comply with study procedures. All the subjects provided written informed consent. Investigators were the primary care pharmacists from the participating sites, and the participants were recruited once they received the first authorized prescription.Patients received GLP1 RA prescriptions from their physicians during normal clinical practice, and pharmacists included them in the homologation process afterward. The inclusion of patients is totally separated from the initial prescriptions of GLP1 RA.

2.3. End points

The primary end point was the weight loss achievement, defined as a weight loss ≥ 5 % of patient́s baseline weight [19]. Weight was measured and recorded on baseline visit and at follow-up (3 months) within a one-week window. If not the weight closest to the follow-up date was used. We also calculated the change of weight loss in kg and the change of BMI from the baseline visit to the follow-up (3 months).

Another co-primary endpoint was the change in HbA1c (% unit) at 3 months. HbA1c was measured and recorded on baseline visit and at follow-up (3 months) within a window of 3 months for the baseline visit, if not the HbA1c closest to the follow-up date was used.

As a secondary endpoint, safety was assessed by monitoring adverse events reported by the investigators on the electronic clinical report form (e-CRF). Data collected at the baseline included information on prescribing physicians and patient demographics and clinical characteristics. Data related to safety outcomes were collected at follow-up visits (week 4, week 8 and week 12). This information was collected through the electronic medical reports (our health system includes

Table 1
Demographic and baseline characteristics.

	All GLP1 (n = 94)	GLP1 RA (n)			
		s.c. semaglutide [40]	oral semaglutide [28]	dulaglutide [21]	Other [5]
Sex (male); n(%)	51 (55.4)	16 (59.3)	13 (61.9)	20 (51.3)	2 (40.0)
Years; mean (SD)	61.9 (10.9)	62.0 (10.6)	62.3 (10.2)	61.4 (11.8)	63.8 (11.6)
Medical history; n (%)					
Diabetic neuropathy	5 (5.4)	0 (0.0)	1 (4.8)	3 (7.7)	1 (20.0)
Diabetic retinopathy	7 (7.6)	2 (7.4)	3 (14.3)	2 (5.1)	0 (0.0)
Biliary disease	8 (8.7)	0 (0.0)	2 (9.5)	6 (15.4)	0 (0.0)
Pancreatitis	2 (2.2)	1 (3.7)	0 (0.0)	1 (2.6)	0 (0.0)
Familiar thyroids	10 (11.0)	2 (7.4)	2 (9.5)	4 (10.5)	2 (40.0)
Hypertension	71 (77.2)	24 (88.9)	16 (76.2)	28 (71.8)	3 (60.0)
Dyslipidemia	73 (79.3)	22 (81.5)	16 (76.2)	30 (76.9)	5 (100.0)
ACS	19 (20.9)	8 (30.8)	6 (28.6)	4 (10.3)	1 (20.0)
Stroke	6 (6.5)	1 (3.7)	1 (4.8)	3 (7.7)	1 (20.0)
HF	12 (13.0)	6 (22.2)	3 (14.3)	3 (7.7)	0 (0.0)
OSAHS	16 (17.4)	3 (11.1)	5 (23.8)	7 (17.9)	1 (20.0)
Asthma or COPD	13 (14.1)	2 (7.4)	4 (19.0)	5 (12.8)	2 (40.0)

*s.c.: subcutaneous. ACS: Acute Coronary Syndrome. HF: Heart Failure. OSAHS: Obstructive Sleep Apnea Hypopnea Syndrome. COPD: Chronic Obstructive Pulmonary Disease.

Table 2
Primary endpoint: change in body weight. Change in HbA1c.

	Total	Medication				p-value
		s.c. semaglutide	oral semaglutide	dulaglutide	Other	
Weight Loss ≥ 5%; n (%)	37/77 (48.1%)	11/24 (45.8%)	11/18 (61.1%)	13/32 (40.6%)	2/3 (66.7%)	0.494
Body Weight Change (-kg); Mean (95%CI)	-4.9 (−6.2; −3.6)	-4.7 (−7.5; −1.9)	-4.9 (−7.9; −1.9)	-5.0 (−6.8; −3.3)	-6.1 (−22.4; 10.2)	0.982
BMI (-kg/m^2); Mean (95%CI)	-1.87 (−2.36; −1.37)	-1.87 (−2.95; −0.81)	-1.82 (−2.95; −0.69)	-1.82 (−2.50; −1.15)	-2.47 (−9.91; 4.97)	0.971
HbA1c (-%); Mean (95%CI)	-1.36 (−1.76; −0.95)	-0.91 (−1.41; −0.41)	-1.36 (−2.46; −0.27)	-1.74 (−2.46; −1.03)	-1.40 (no data)	0.383

*s.c.: subcutaneous. BMI: Body Mass Index.

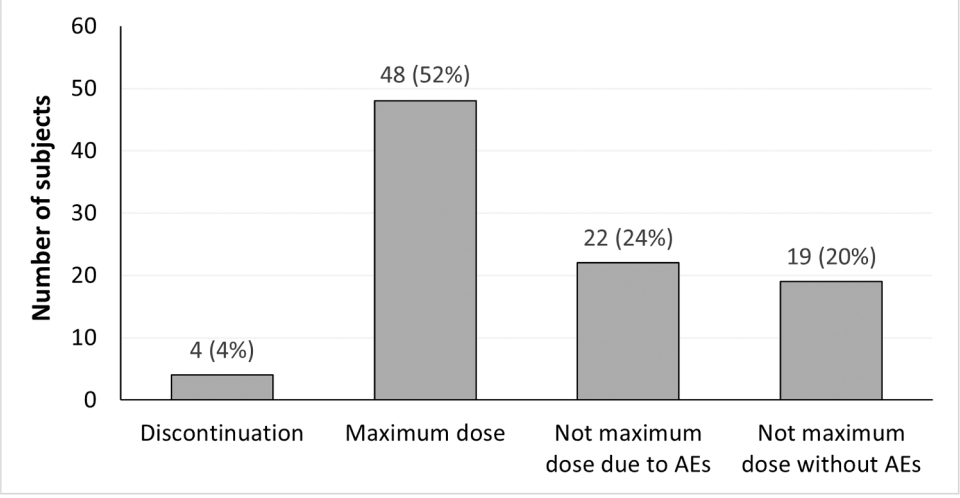

Fig. 1. Tolerance and discontinuations from GLP1 RA treatments.

adverse events reports from the primary care system to hospital specialists) and it was also collected through direct interview calls with the patients.

The assessment for adherence was based on the proportion of days covered (PDC) [20]. PDC is defined as the number of days covered by a GLP-1 RA prescription divided by the number of days during the measurement period. Patients were classified as adherent if the PDC was ≥ 0.80 at these time points. Discontinuations and change of doses, due to adverse events, were also collected by the investigators through the previously described methods.

2.4. Statistical analysis

A descriptive analysis expressing the continuous variables in mean and standard deviation (SD) and qualitative variables in absolute and relative frequencies were performed.

To evaluate differences in weight, BMIand HbA1c reduction between baseline and follow-up we used Student́s t test for paired samples, and to

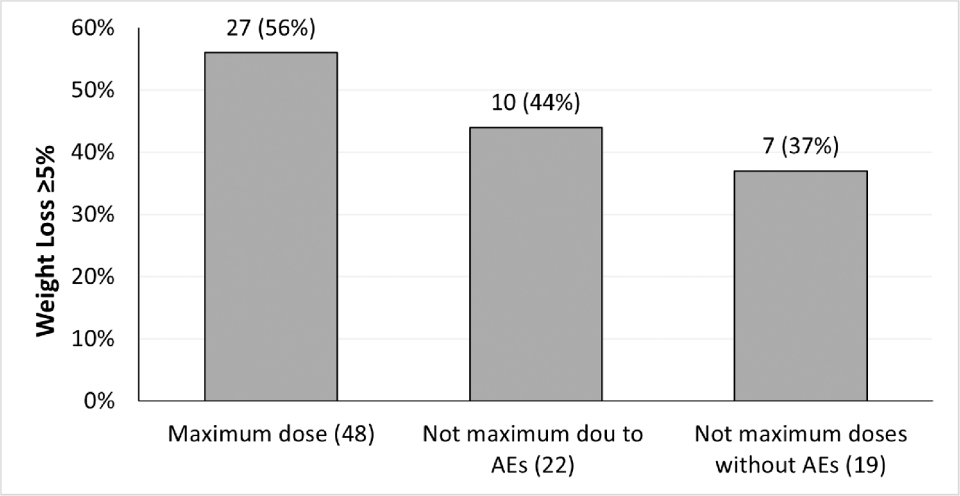

Fig. 2. Weight loss ≥5% by dose or tolerance.

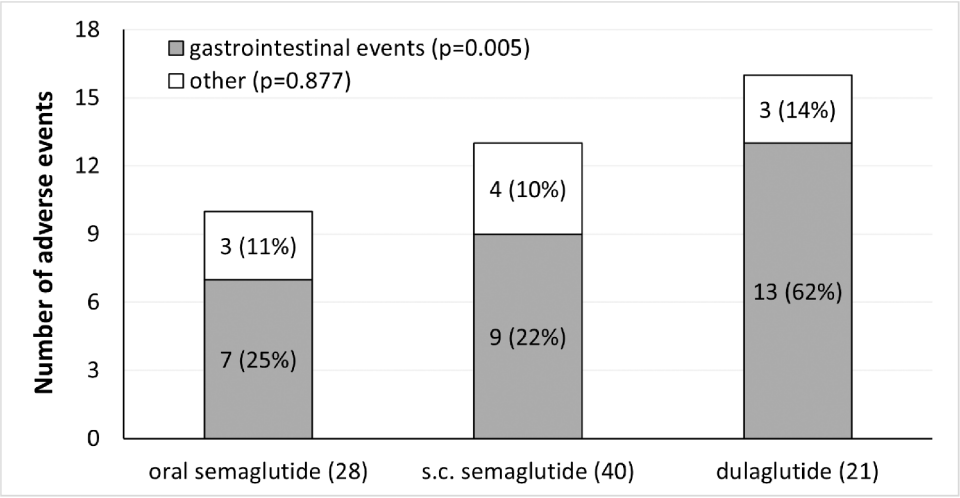

Fig. 3. Safety: adverse events. Gastrointestinal events and other events.

detect differences between different GLP1 RA we carried out one-factor analysis of variance (ANOVA). The analyses were performed with the software SPSS version 19.

As it was not feasible to include the complete estimated sample in the initial protocol, statistical power analysis was conducted using G*Power software to determine the main endpoint determinations. For comparing weight, BMI, and Hba1c variations between the initial and final period for the entire sample, the statistical power was above 95 % for all comparisons. However, for group comparisons, the power varied from 16 % and 20 % for weight and BMI comparisons to 83.9 % for the Hba1c comparison. Regarding adverse events (AEs) comparisons between the s.c. semaglutide, oral semaglutide, and dulaglutide groups, the statistical power for gastric abnormalities was over 80 %, while for other abnormalities, it was 7 %.

3. Results

3.1. Study participants

A total of 94 patients met the inclusion criteria and were included in the study. Weight measurements were available for 77 patients at 3 months. Among the 94 patients initiating a GLP-1 RA, 42,4 % received *dulaglutide*, 29,3 % *subcutaneous semaglutide*, 22,8 % *oral semaglutide* and 5,4 % other GLP1 RA.

3.2. Demographics and baseline characteristics

The three main treatment groups had similar demographics and baseline characteristics (Table 1). Among the participants, 45 % were female and the mean age was 62 years. The mean (SD) body weight, BMI, and waist circumference were 99.3 (19.2) kg, 36.7 (5.9) kg/m2, and 118.6 (14.0) cm, respectively. At baseline, the mean (SD) Hba1c and serum glucose were 8.2 % (1.3) and 173.1 mg/dL (53.3), respectively. The majority of patients had hypertension and dyslipidaemia, and some had a history of ACS or heart failure. A subset of patients also had other T2DM complications or related pathologies (see Table 1).

3.3. Primary end point: change in body weight

Among patients who had weight determinations at 3 months, nearly 50 % of all patients lost ≥ 5 % of their baseline weight. *Oral semaglutide* achieved the highest reduction with 61,1 % of patients achieving ≥ 5 %. *Subcutaneous semaglutide* 45,8 % and *dulaglutide* 40,6 %. GLP1 RA significantly reduced body weight (MD −4.95 kg; CI (−6.2; −3.6) $p <$ 0.001). The change in body weight from baseline to month 3 were − 5.0 kg in the *dulaglutide* group, − 4.9 kg in the *oral semaglutide* group and −

4.7 kg in the *subcutaneous semaglutide* group, there were no statistically significant differences between groups ($p = 0.982$). GLP1 RA significantly reduced BMI (MD −1.86 kg/m^2; CI (−2.36; −1.37) $p < 0.001$). BMI was reduced from baseline to follow-up visit by − 1.87 kg/m^2 in the *subcutaneous semaglutide* and by − 1.82 kg/m^2 in other both groups (*dulaglutide* and *oral semaglutide*), but no statistically significant differences were found among the 3 treatment groups ($p = 0.971$). (Table 2).

3.4. Change in HbA1c

Among patients who had HbA1c, and serum glucose measured at 3 months (N = 60; N = 69), GLP1 RA significantly reduced HbA1c (MD −1.4 %; CI (−1.76; −0.95) $p < 0.001$) and glucose (MD −48.7 mg/dL, $p < 0.001$). There were no statistically significant differences between groups for both parameters ($p = 0.383$) (Table 2).

3.5. Secondary end points: adherence and safety

All the patients adhered to the treatment regimen, and none of them scored a PDC≤ 80. The overall proportion of patients who discontinued GLP1 RA therapy was 4 % at 3 months, whereas 52 % of all patients reached the maximum dose at month 3; 24 % of all patients did not achieve the maximum goal dose objective due to intolerance, but 20 % of the patients did not titrate up to the highest dose despite adequate tolerance; 55,8 % of patients that receiving maximum dose of GLP1RA lost ≥ 5 % of their baseline weight whereas only 37,5 % of patients that did not achieve the maximum dose of GLP1RA lost ≥ 5 % of their baseline weight (Fig. 1 and Fig. 2).

Regarding the adverse events (AEs), 47 events were reported. Gastrointestinal disorders (nausea, diarrhoea, constipation, dyspepsia, etc.) were the most frequently reported events (N = 35; 74,5 %) and occurred in more participants receiving *dulaglutide* than those receiving *oral semaglutide* and *subcutaneous semaglutide* (62 % vs. 25 % vs. 22 %). Other mild events (N = 11) were reported in minor proportion (headache, nauseas, or injection reaction), 14 % in participants receiving *dulaglutide*, 10 % *subcutaneous semaglutide* and 11 % *oral semaglutide*. One patient under dulaglutide presented a cardiovascular death. (Fig. 3).

4. Discussion

In this multicenter prospective study, we found that during the initial titration phase, 3 of the GLP1 RA evaluated were associated with a significant weight loss although with some differences between these three drugs. Overall, it can be said that almost 50 % of the patients achieved a weight loss ≥ 5 %. Moreover, all GLP1 RA significantly reduced HbA1c without differences among groups. However, it need to be highlighted that 20 % of the sample did not reach the maximum dose at month 3 despite adequate tolerance. Finally, *dulaglutide* presented a significantly higher rate of gastrointestinal disorders than *oral* and *subcutaneous semaglutide*. From our point of view, these results could be relevant not only at the time of GLP1 RA prescriptions but also at the time of cardiovascular events reduction shown in the pivotal studies.

Our population shares demographics and baseline characteristics with the main pivotal studies with GLP1 RA. Hypertension was reported by 77,2 % of all patients, 79,3 % had dyslipidaemia, 20,9 % previous acute coronary syndrome (ACS) and 13,0 % heart failure. Considering the CV high risk of this population, we could suggest initiating these drugs earlier than they are being prescribed. Moreover, the patients included had a mean (SD) body weight of 99.3 (19.2) kg, a mean (SD) BMI 36.7 (5.9) kg/m^2, a mean (SD) waist circumference 118.6 (14.0) cm, a mean (SD) Hba1c 8.2 % (1.3) and a mean (SD) serum glucose 173.1 mg/dL (53.3) which shows that we are initiating GLP1 RA in patients with very advanced obesity and T2DM. For this reason, we opine that GLP1 RA might be prescribed too earlier than they are, and patients with these characteristics could benefit from an earlier start. On the other hand, only 7,6 % of all patients presented diabetic retinopathy, 8,7 % presented previous history of biliary disease, 2,2 % pancreatitis and 11,0 % previous familiar thyroids disease, which shows a high adherence to the summary of product characteristics.

Subcutaneous semaglutide has been investigated in the SUSTAIN trials [9–13], which showed significant reductions in HbA1c, and body weight compared to placebo and other GLP1 RA. *Subcutaneous semaglutide* reduced body weight from − 2.50 kg to − 4.15 kg. Other clinical trials have examined the efficacy and safety of *oral semaglutide* in terms of reducing HbA1c and body weight in individuals with T2DM as reported by the PIONEER studies [21–24]. *Oral semaglutide* reduced body weight from − 0.53 kg to − 3.18 kg. Moreover, 14.0 mg *oral semaglutide* was superior to another GLP1 RA comparator in reducing body weight by − 2.42 kg. The LEADER [25] was a clinical trial with liraglutide where the difference between *liraglutide* and placebo in weight loss was 2.3 kg. *Dulaglutide* showed changes in weight in the AWARD-11 trial [26]. For the efficacy, patients whose *dulaglutide* dose was increased from 1.5 mg to the 3.0 mg and 4.5 mg doses had greater reductions in body weight compared to those stayed on *dulaglutide* 1.5 mg from 12 weeks, with superior weight loss for 3.0 mg (−4.0 kg) and 4.5 mg (−4.7 kg). An analysis of the effects of *exenatide* [27] over 82 weeks reported that patients taking *exenatide* in dual therapy with *metformin* experienced weight loss. Reduction in body weight was progressive, with a change from baseline of − 4.4 kg at week 82. However, there is a paucity of clinical trial evidence comparing the efficacy and adverse effects of different GLP1 RA treatments with each other. Also, although randomized trials of GLP-1 RA have demonstrated clinically significant weight loss, weight loss has not been widely characterized using real-world data in patients naïve to GLP-1 RA therapy. A recent study in patients with type 2 diabetes initiating GLP1 RA in the UK showed that a minority of patients initiating GLP1 RA achieved ≥ 5 % weight loss (34 % of all patients at month 12), suggesting the real-world benefit of these agents on weight loss may be lower than that observed in clinical trials [14]. In our study, nearly 50 % of patients achieved ≥ 5 %weight loss. One of the reasons could be that in our region these prescriptions require approval by pharmacists and these patients receive close follow-up, and as a result, the adherence and discontinuations were lower than reported in the above-mentioned studies. On the other hand, our study had a shorter follow-up (3 months), one of the limitations of the analysis. However, if we compare our study with the STEP study [28], we found that even though both populations had similar demographics and baseline characteristics, in the STEP trial, 86 % of the patients achieved ≥ 5 % weight loss during the 68 weeks of follow-up, higher than those seen in our study despite good adherence and fewer discontinuations. One potential explanation could be that participants of clinical trials tend to be more motivated to comply with the treatment regimens assigned by the investigators. In contrast, in the pivotal clinical trials, in our environment, 20 % of patients are not taking maximum doses despite good tolerance, in sharp contrast what was reported in STEP [28] and LEADER [25] for instance, by the mere fact of being included in the trials.

A systematic review and network meta-analysis recently published (n = 27,000 patients) reported that *semaglutide* (subcutaneous and oral) and *liraglutide* were the most efficacious GLP1 RA for weight loss at 12 weeks of follow-up [29]. These results are in line with our study. The second relevant meta-analysis (n = 7000 patients) showed that there were no statistically significant differences between *semaglutide* (subcutaneous and oral) and *liraglutide* [30], similar to our study, but this meta-analysis presented the limitation that they included retrospective studies, and they did not report the percentage of patients achieving ≥ 5 % weight loss. From our point of view, because that weight loss between 5 % and 7 % of body weight is known to improve metabolic control and reduce the risk of developing cardiovascular disease [7], we used this variable as an endpoin. Relevantly, *oral semaglutide* had a higher proportion of patients achieving ≥ 5 % of weight loss than *subcutaneous semaglutide* and *dulaglutide* (61,1 % vs. 45,8 % vs. 40,6 % respectively).

Regarding the weight loss in kg and changes of BMI we did not find statistically significant differences between different GLP1 RA, possibly

due to the small sample size and a shorter follow up. We found a significant body weight reduction (MD −4.95 kg, $p < 0.001$) and a significant BMI reduction (MD −1.86, $p < 0.001$), higher than those reported in the SUSTAIN [9–13] and PIONEER [21–24] trial and meta-analysis but lower than in the STEP [26] trial.

The overall reduction in HbA1c and serum glucose at 3 months were also statistically significant: HbA1c (MD −1.4 %, $p < 0.001$) and glucose (MD −48.7 mg/dL, $p < 0.001$), and they were very similar to those in the pivotal clinical trials and even higher with *oral semaglutide*. This early target in the glycaemic control could be the reason that 20 % of the patients were not taking maximum doses of GLP1 RA. One possible reason could be the saturation of the primary health care system, where the patients do not receive monthly follow-up as required by the titration. Another potential reason could be related to the glycaemic control alone and not the degree of weight loss. Importantly, the importance of increasing doses is shown in our results: 56 % of patients taking maximum doses achieved ≥ 5 % of weight loss whereas 37 % of patients with good tolerance and taking medium doses did not achieve ≥ 5 % of weight loss. Only 4 % of the patients discontinued the treatment but this could be explained by the short follow-up (3 months). In our study, the adherence to the treatments among the remaining patients ranged from 80 % to 100 % according to the PDC formula [20]. This is in sharp contrast with previous observational studies that showed an adherence of 65 % [16]. Moreover, 24 % of the patients did not reach the maximum doses due to intolerance. High adherence to these drugs in Spain can be explained by their compliance with sanitary approval. Patients who are suitable for GLP1RA are closely monitored, and adherence to treatment is one of the prescription criteria. Investigators could obtain data by reviewing electronic medical records. An entry with the date and time in the medical record can be checked to determine when patients obtained medication from pharmacies.

Gastrointestinal disorders were the most frequently reported events (74,5 %). According to treatments, 62 % of the patients receiving *dulaglutide* experienced some sort of gastrointestinal adverse event, 25 % of those receiving *oral semaglutide* and 22 % of *subcutaneous semaglutide*. Other mild events (N = 11) were reported in minor proportion (headache, nauseas, or injection reaction), 14 % in participants receiving *dulaglutide*, 11 % on *oral semaglutide* and 10 % on *subcutaneous semaglutide*. These findings do not align well with the results of *Kia Vosoughi* et al. [29], perhaps due to the small follow-up, but more in the direction of the REALISE-DM Study [31] where authors reported a smaller number of adverse events. Taking into account the results of the REALISE-DM Study that indicates that switching to *subcutaneous semaglutide* from *liraglutide* or *dulaglutide* is associated with further reductions in HbA1c, weight, and BMI in patients with T2DM and also that this switch may help to improve patient adherence if the switch is from daily subcutaneous GLP1 RA injections and based on our results where we obtained a higher efficacy and safety with *oral semaglutide*, a reasonable option could be to switch to *oral semaglutide*.

We acknowledge that our study has several limitations. One limitation of our study is that we did not take into account other antidiabetic drugs. We minimized this bias by the Spanish funding criteria for GLP1 RA, which require the concomitant use of metformin, and we assumed that other antidiabetic drugs did not affect weight loss (the primary outcome). Regarding lifestyle interventions, all patients received dietary and exercise advice at each study visit. Another limitation of this study was the low number of prescriptions of other GLP1 RA (including *liraglutide*), which were only five cases. However, this reflects the reality of a real-world study and shows the clinical practice accurately. The study has the inherent limitations of a nonrandomized study with a small number of patients, furthermore the initial calculation estimated the inclusion of 360 patients in the study, but due to supply problems with these medications in our region, the inclusion rate was affected, and we were only able to include 94 subjects who met the inclusion criteria during the study period, furthermore, the patient count for each analysis varied as a result of some individuals being lost to follow-up, which is an inherent characteristic of real-world studies As limitations, due to the study design where we focused only on the titration phase, the follow-up is shorter than other studies and we analysed a small sample size, therefore further investigations in this direction are needed, including new analogues with dual glucose-stimulated insulinotropic peptide agonist, *tirzepatide*, which showed a mean percentage change in weight at week 72 by − 15.0 %, with 5-mg weekly doses of tirzepatide; by − 19.5 % with 10-mg doses; and by − 20.9 % with 15-mg doses [32].

5. Conclusions

To our knowledge, this study is one of the first prospective real-world studies in patients with T2DM and obesity who achieved clinically significant weight loss (≥5 %) besides clinically significant changes in weight (kg) and HbA1c (%). *Oral semaglutide* achieved the highest proportion of patients that lost ≥ 5 %. A small group of patients (4 %) discontinued the treatment, a quarter of patients were unable to titrate doses due to adverse events but 20 % of patients did not reach maximum doses despite good tolerance, this group of patients could benefit from higher titration doses. Most of the reported adverse events were gastrointestinal disorders and they occurred more frequently in the *dulaglutide* group. *Oral semaglutide* would be a reasonable switch in case of future shortages.

Author statement

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Declaration of Competing Interest

Authors declare that there are no conflicts of interest related to the results of this study. Jose Seijas Amigo reports consulting fees from Astra Zeneca. All authors accept the rules of the announcement.

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Appendix 1

See Tables 1 and 2.

Appendix 2

See Figs. 1–3.

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