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Effectiveness and Safety of Weekly Subcutaneous Semaglutide for Weight Management in Obese Adolescents: An Observational Study

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Abstract

We aimed to evaluate effectiveness and safety of weekly subcutaneous (sc) semaglutide for weight reduction, along with diet and lifestyle modifications in severely obese adolescent patients attending an Obesity Unit.

In a prospective observational study, 21 severely obese adolescent patients (18 females, mean age 14.95 years, mean baseline body mass index 33.01 kg/m^2) were followed for 8.0 months (median) after initiation of sc semaglutide in two different private institutions. Starting dose and dose titration were decided according to best clinical judgement and based upon effectiveness and gastrointestinal tolerance.

At final office visit patients averaged a weight loss of 8.32 ± 7.65 kg (8.68 ± 7.76% baseline body weight). Starting dose was 0.23 mg and final dose was 0.68 mg. Two patients prematurely discontinued treatment and one patient was lost from follow-up. Nausea and abdominal pain at the beginning of treatment were reported by 10 (47.61%) and 5 (23.81%) patients, respectively. One patient had a vomiting episode and another complained from diarrhoea. No other safety issues were noted.

Out-of-label weekly administration of (sc) semaglutide with a *sui-generis* titration scheme resulted in a clinically significant and safe weight loss in obese adolescents. Initial nausea and abdominal pain were frequently reported. Magnitudes of weight loss and safety profile were similar to those of adult population, yet with lower doses. Weekly administration of (sc) semaglutide is a promising adjunct therapy to standardised model of care of children and adolescents with obesity that deserves further evaluation to confirm safety and efficacy.

Keywords: Observational study; Adolescent obesity; GLP-1 analogue; Subcutaneous semaglutide

Abbreviations: ADHD: Attention Deficit and Hyperactivity Disorder; BMI: Body Mass Index; GI: Gastrointestinal GLP-1a: Glucagon-like Peptide 1 agonists; Sc: Subcutaneous; SD: Standard Deviation

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Introduction

Obesity rates have increased sharply over the past 30 years [1], especially among children and adolescents [2]. Obesity in the youth is associated with a rise in comorbidities previously identified in the adult population, such as Type 2 Diabetes Mellitus, Hypertension, Non-alcoholic Fatty Liver disease, Obstructive Sleep Apnoea, and Dyslipidemia [3,4]. So far, interventions for overweight/obesity prevention and treatment in this age group have mainly focused on behavioural changes such as increasing physical exercise or improving quality of diet and/or restriction of calorie intake [5,6]. However, these efforts frequently lead to

limited and not sustained results and pharmacotherapy and/or bariatric surgery remain a necessary option for those adolescents with more severe obesity [7]. In this sense, recent findings from an interventional drug trial utilizing liraglutide, a GLP-1 agonist with a daily dose, have demonstrated successful weight loss in obese adolescent patients [8].

In this observational study, we aimed to evaluate effectiveness and safety of weekly administration of subcutaneous (sc) semaglutide in a group of adolescent patients with obesity attending an Obesity Unit in two private institutions in Mallorca (Spain), along with dietary and lifestyle recommendations.

Materials and Methods

In this observational prospective study, patients 18 years old or less attending an Obesity Unit in two different private institutions who started on subcutaneous (sc) semaglutide since May 2020 were consecutively invited to take part in the study and after obtaining written informed consent from patients and legal tutors when applicable. Due to the observational nature of this study, no protocol was submitted for Ethics Board approval.

After a throughout shared decision process involving patients and legal tutors in which comprehensive information regarding potential benefits and harms of subcutaneous (sc) semaglutide use were reviewed, a total of 21 patients were consecutively included in the study. All patients were prescribed subcutaneous (sc) semaglutide with an out-of-label indication for weight reduction, as part of a structured program for the management of overweight and/or obesity that included initial medical evaluation, laboratory examinations when clinically indicated, diet and exercise counselling and regular follow-up office visits. Diet counselling included in most cases a structured quantitative dietary recommendation with an average 500 kcal/day reduction from calculated baseline metabolic rate adjusted by physical activity.

Height, weight, and Body Mass Index (BMI) were recorded as baseline variables at initial visit. Pubertal development was evaluated according to Tanner Stages and medical history including both eating behaviour and mood disorders was also registered. At baseline visit, subcutaneous (sc) semaglutide was started at a dose of 0.25 mg once weekly in most cases, (unless otherwise indicated by best clinical judgement), according to label instructions, but subsequent dose titration was conducted under physicians' judgement based primarily upon safety and Gastrointestinal (GI) tolerance (namely, incidence of nausea, vomiting or abdominal pain) and additionally upon weight reduction response. The study was prolonged until all patients reached a minimum follow-up of 6 months.

Primary effectiveness outcome in this study was absolute and percentage weight loss from baseline after initiation of subcutaneous (sc) semaglutide until last available follow-up visit. Secondary objectives included incidence of non-serious/serious adverse events and/or GI adverse events, proactively referred to by patients.

Statistical analysis

All data are expressed as mean ± Standard Deviation (SD) for continuous variables, median and interquartile range for follow-up period and as percentage for categorical variables. Because this is an observational study, no statistical comparisons were performed beyond descriptive analysis, except for primary effectiveness outcome using a Student T-test with a p level of significance <0.05.

Results

Table 1A show baseline characteristics of patients included in this study. A total of 21 patients completed a first follow-up visit. One patient refused to maintain the treatment after two weekly doses of 0.25 mg because of intense abdominal pain and was excluded from effectiveness analysis. On average, patients had a mean age of 14.95 ± 2.33 years and a wide majority of them were females (n 18; 85.71%). Mean BMI was 33.01 ± 4.50 kg/m^2, with only two patients with a BMI below the 95 percentile (overweight) and all the rest with a BMI over the 99 percentile (severe obesity). One 10-year-old male patient had a prepubertal Tanner I stage, six female patients had a recent onset pubertal development (Tanner II-III) and 13 females and one male patient had a well-developed puberty (Tanner IV-V).

Regarding medical history, a 10-year-old male patient was diagnosed with severe ADHD (Attention Deficit and Hyperactivity Disorder) and a 17-year-old female patient had Down syndrome plus hypothyroidism. Eight patients (38%) had a previous diagnosis of disordered eating behaviour (either Bulimia Nervosa or Binge Eating Disorder) and 4 patients had been diagnosed with either Anxiety or Depressive Disorder. Three patients were currently receiving antidepressant medication (fluoxetine or escitalopram) and an additional patient with a BMI of 45.2 kg/m^2 was on metformin 850 mg bid, without a previous diagnosis of Diabetes.

Laboratory examinations did not reveal any potential contraindication for subcutaneous (sc) semaglutide use. Conversely, elevated triglycerides, uric acid and liver enzyme

Table 1 A) Baseline characteristics of patients.

Variables	Total
N	21
Sex (female, %)	85.71
age (years), ± SD¶	14.95 ± 2.33
Height (cm), ± SD	165.33 ± 6.87
Baseline body weight (kg), ± SD	90.01 ± 15.61
Baseline BMI‡ (kg/m^2), ± SD	33.01 ± 4.50
Tanner stage I-V (n)	
Tanner I	1
Tanner II-III	6
Tanner IV-V	14
Bulimia nervosa (n, %)	5 (23.8%)
Binge-eating disorder (n, %)	5 (23.8%)
Anxiety disorder	3 (14.3%)
Depressive mood disorder	1 (4.7%)

tests, high fasting insulin plasma levels and borderline fasting glucose levels were common findings in those patients with higher BMI values.

Weight reduction

Table 1B shows changes in body weight (absolute and percentage *vs.* baseline) by the last available follow-up office visit. After a median follow-up of 8 months (interquartile range, 6-11 months) 20 patients had achieved a mean weight loss of 8.32 ± 7.65 kg (8.68 ± 7.67% of baseline body weight), with only one patient having actually gained weight.

Mean final semaglutide dose was 0.68 ± 0.22 mg. Only three patients arrived to the 1 mg dose, while most patients remained in the 0.5 mg weekly dose. No de-escalation of dose was performed in any patient due to GI intolerance or other safety concerns.

Safety and tolerability

An 18-year-old female patient refused to maintain semaglutide treatment after two consecutive weekly injections of 0.25 mg, due to the appearance of moderate to intense abdominal pain. Another 13-year-old female patient was lost from follow-up after 4 months with an actual weight loss of 6.55% of baseline body weight and a third 18-year-old male, stopped semaglutide treatment due to economic constraints, after a weight loss of 18 kg (18% *vs.* baseline). **Table 1B** reflects incidence of GI symptoms. Abdominal pain (n 5; 23.81%) and nausea (n 10; 47.61%) were commonly referred to by patients, especially during the first month of treatment. In most cases, light meals, proper hydration and occasional use of antacids (oral omeprazole) were enough measures to solve the episodes and ensure continuation of treatment. In some of these patients, restoration of treatment with semaglutide included a transient de-escalation of dose to avoid further episodes, along with a reinforcement of dietary counselling.

Discussion

In this observational study we evaluated weight reduction associated to out-of-label use of subcutaneous (sc) semaglutide in a group of paediatric and adolescent patients, most with severe obesity as part of a pragmatic strategy for weight management. After more than six months of follow-up, a clinically significant (>5%) weight loss of 8.68% was reached with an average subcutaneous (sc) semaglutide weekly dose of 0.6 mg. Abdominal pain and nausea were frequently reported by patients, but did not result in treatment abandon in most cases. No other safety concerns were noted in this group of under aged patients in which, obviously, safety always comes first.

Table 1 B) effectiveness and GI[§] tolerance outcomes.

Variables	Total
Weight Loss (kg), mean ± SD	8.32 ± 7.65*
% Weight Loss (%), mean ± SD	8.68 ± 7.67*
Follow-up (months) median, ICR[ǂ]	8.0 (6-11)
Semaglutide final dose (mg), mean ± SD	0.68 ± 0.22
Treatment withdrawal (n, %)	3 (15.0%)
GI symptoms (n, %)	
Nausea	10 (47.61%)
Vomiting	1 (.76%)
Diarrhoea	5 (23.81%)
Abdominal pain	1 (4.76%)

[§]Gastrointestinal
[¶]Standard Deviation
[ǂ]Body Mass Index
*p<0.05 vs baseline body weight
[ǂ]Interquartile range

Obesity in the early stages of life represents an important public health problem, with increasing rates of metabolic comorbidities [9]. Furthermore, up to 70% adolescents with obesity will have the same condition as adults [10]. Also, adolescent obesity not only implies potential metabolic comorbidities, but also a low self-esteem, suboptimal quality of life and mood disorders [11].

In May 2020, Kelly AS, et al [8] published the results of a randomized trial evaluating for the first time, the efficacy and safety of liraglutide 3.0 mg once daily plus lifestyle therapy, for weight loss in obese adolescents. A 5.01% weight change was observed *vs.* placebo after 52 weeks of treatment and nausea, vomiting and abdominal pain were reported more frequently than in adult population, although weight change was somewhat inferior. Nevertheless, by December 2020, FDA approved Liraglutide 3.0 mg once daily for the management of obesity in adolescents older than 12 yr. Subcutaneous semaglutide is currently undergoing a clinical development program for obesity (The Semaglutide Treatment Effect in People with obesity - step). Published results from trials step-1 and step-4 range between 7.9 to 14.9% weight loss *vs.* baseline in adults with a 2.4 mg weekly dose [12,13]. An ongoing 68-week randomized trial is dedicated to evaluate efficacy and safety of subcutaneous (sc) semaglutide titrated to 2.4 mg once weekly in adolescents with overweight or obesity. The study is expected to be completed by March 2022 [14].

We have previously reported for the first time on effectiveness of subcutaneous (sc) semaglutide (0.5 to 1.0 mg once weekly) in obese and overweighed adults in a real-world setting with a 9.13% median weight loss after 10.7 months of follow-up with a high therapeutic adherence [15]. Now we report on a similar therapeutic strategy in severely obese adolescents, with similar dose-adjusted results compared to adult patients from our study and superior to those seen in the liraglutide trial in adolescents.

Additionally, the prevalence of both eating and mood disorders among adolescent patients with obesity is higher than in the general population, as it was the case in this patients group. It is known that these psychological comorbidities can influence the results of different obesity treatment interventions [16]. In this sense, liraglutide has shown beneficial effects on emotional eating, dietary disinhibition, global eating disorder psychopathology and shape concerns [17]. Recently, semaglutide 2.4 mg weekly improved control of eating and reduced food cravings among adults with obesity, possibly due to the effects of this molecule on hedonic and homeostatic control of eating [18].

Conclusion

Our study represents the first published observational evidence for effectiveness and safety of subcutaneous (sc) semaglutide with a weekly administration in the management of overweight and obesity in adolescents in a real-world setting. It is not usual that an observational study reporting on effectiveness and safety of a drug in real practice conditions is published before gaining regulatory approval for the specific indication, as efficacy and mostly safety are important issues that must be first addressed by randomized clinical trials, and the authors deeply acknowledge this fact. Nevertheless, several important questions must be kept in mind in this regard; first, subcutaneous (sc) semaglutide has now evidence for efficacy and safety in non-diabetic obese adults and a regulatory approval for use in this setting is expected. Second, liraglutide, a GLP-1 analogue with a similar molecular design and pharmacological properties has been approved for weight reduction in obese adolescents over 12 years old and third, given the shortage of effective treatments to treat obesity in this young population, the authors believe that evidence provided by this study is timely, and of scientific interest. Given the limitations of an observational study, we will need to confirm these results with the forthcoming results of the STEP program trial in adolescents and contrast them with results from other groups in a real practice setting which for sure will be coming up in future. Until then, we consider that weekly subcutaneous (sc) semaglutide represents a useful and safe tool for helping adolescent patients in their long-term struggle, along with diet and lifestyle changes, to increase their chances to arrive to and maintain a healthy body weight.

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