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EDITORIAL

Unraveling the safety and efficacy of semaglutide for people living with HIV and metabolic co-morbidities

Dimitrios Patoulias[a], Paschalis Karakasis[b], Ieva Ruža[c], Mohamed El-Tanani[d] and Manfredi Rizzo[d,e]

[a]Second Propedeutic Department of Internal Medicine, Faculty of Medicine, School of Health Sciences Aristotle, University of Thessaloniki, Thessaloniki, Greece; [b]Second Department of Cardiology, Faculty of Medicine, School of Health Sciences Aristotle, University of Thessaloniki, Thessaloniki, Greece; [c]Department of Endocrinology, Riga East Clinical University Hospital, Riga, Latvia; [d]Pharmacy, Ras Al Khaimah Medical and Health Sciences University (RAKMHSU), RAK, United Arab Emirates; [e]School of Medicine, Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties (Promise), University of Palermo, Palermo, Italy

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1. Introduction

Human Immunodeficiency Virus (HIV) epidemic is steadily improving, but still challenging, in the context of significant geographical and ethnic disparities; in 2022, there was an estimated number of 39 million people living with HIV (PLWH) worldwide [1]. Of importance, especially since the introduction of the -otherwise life-saving- antiretroviral therapy (ART), the shifting demographics and the increase in life-expectancy, along with physical inactivity and increased caloric intake, compared to previous decades, PLWH experience a significant increase in the risk of metabolic dysregulation, ultimately resulting in the development of overweight/obesity and diabetes mellitus (DM), and thus, in related complications [2].

Prevalence of overweight and obesity among PLWH appears to be similar to that observed in the general population; according to recent evidence, one-third of PLWH are classified as overweight, whereas 8.3% of them are considered to be obese [3]. In addition, the prevalence of overweight/obesity among PLWH has increased from 29.4% in 2005 to 39.6% in 2015, documenting the presence of the increasing trend of overweight/obesity among PLWH, as also seen in the general population [3]. Male gender, older age, use of protease inhibitors, and low CD4 count have been shown to be inversely associated with obesity in that population [3]. Concerning the incidence of DM, recent data suggest a cumulative incidence rate of 4.9%of overt DM and a cumulative incidence rate of 14.9% of prediabetes among PLWH, whereas global age-standardized DM prevalence in the general population is 6.1% [4]. Major risk factors for DM development among PLWH include progressive aging, family history of DM, presence of overweight/obesity, Black or Hispanic race, lipodystrophy, metabolic syndrome, and specific ART regimens [4]. Of course, it has to be highlighted that there are significant differences and heterogeneity in the prevalence of obesity and DM among PLWH across different geographic regions and ethnicities, finding that it is compatible with what is also observed in the general population.

Besides overweight/obesity and DM, PLWH experience a significant increase in the risk for development of other dysmetabolic co-morbidities, such as metabolic dysfunction-associated steatotic liver disease (MASLD), compared to the general population, which further increases overall morbidity and mortality. Indeed, the overall pooled prevalence of fatty-liver disease among PLWH ranges between 33% and 42% [5,6], similar to that observed in the general population. Besides certain risk factors for MASLD in PLWH, including male gender, overweight/obesity, DM, hypertension, dyslipidemia, and metabolic syndrome, duration of ART has also been shown to be an important risk factor for the development of MASLD in that population [6]. Therefore, identification of MASLD in PLWH and implementation of appropriate therapeutic strategies appear to be of paramount importance.

This metabolic dysregulation observed among PLWH over the last decades has resulted in an increased cardiovascular disease (CVD) burden in this population; PLWH are twice as likely to experience development of CVD compared to individuals with HIV, according to a recent, relevant meta-analysis in the field, while, the global population-attributable fraction from CVD attributable to HIV has increased from 0.36% to 0.92% over the last 26 years, a finding indicative of the increased incidence of various forms of CVD among PLWH [7]. Of note, PLWH might also experience an increased risk for chronic kidney disease (CKD) development, with the estimated prevalence of CKD ranging from 4.8% to 12.3% in this population, compared to an age-standardized prevalence of CKD of approximately 10.6% in the general population [8]. Therefore, it is of utmost importance that HIV treatment programs and relevant treatment guidelines encompass newer treatment strategies for mitigating the risk for dysmetabolism and related cardiovascular and renal complications among PLWH.

CONTACT Dimitrios Patoulias dipatoulias@gmail.com Second Propedeutic Department of Internal Medicine, General Hospital "Hippokration", Konstantinoupoleos 49, Thessaloniki 54642, Greece

1.1. Therapeutic role of semaglutide in dysmetabolism

Semaglutide is considered to be one of the most potent and safe drugs in our era, belonging to the class of glucagon-like peptide-1 (GLP-1) receptor agonists [9]. Semaglutide is a once-weekly GLP-1 receptor agonist, administered subcutaneously, with official approval by the United States Food and Drug Administration (FDA) for the treatment of both type 2 DM and obesity; indeed, the FDA approved semaglutide for the treatment of type 2 DM in December 2017, while, in June 2021 semaglutide was also FDA approved for the therapeutic management of obesity regardless of the presence of concomitant type 2 DM. It has to be emphasized that the maximum dose of semaglutide for the treatment of type 2 DM is 1.0 mg once-weekly, whereas the corresponding maximum dose for the treatment of obesity is 2.4 mg once-weekly.

Semaglutide has established cardiovascular efficacy among individuals with type 2 DM and at high cardiovascular risk, according to the results of the formerly published SUSTAIN-6 trial, which documented that treatment with semaglutide 1.0 mg once-weekly versus placebo led to a significant 26% decrease in the risk for the primary composite cardiovascular endpoint, primarily driven by a significant 39% decrease in the risk for non-fatal stroke [10]. According to data retrieved from the recently published FLOW trial, enrolling adults with type 2 DM and CKD, treatment with semaglutide 1.0 mg once-weekly versus placebo offered a significant 24% reduction in the risk for the primary composite renal endpoint, also demonstrating a significant reduction in the risk for cardiovascular death by 29%, a finding not previously shown in the SUSTAIN-6 trial [11].

Semaglutide has demonstrated cardiovascular efficacy even among individuals with obesity without concomitant type 2 DM, as shown in the dedicated SELECT trial; treatment with semaglutide up to 2.4 mg once-weekly resulted in a significant reduction in the risk for the primary composite cardiovascular endpoint by 20%, also offering a significant 18% reduction in the risk for the composite heart failure (HF) endpoint and a significant 19% reduction in the risk for all-cause death, compared to placebo [12]. Those results are in line with results generated by recent trials assessing the safety and efficacy of semaglutide 2.4 mg once-weekly in individuals with HF with preserved ejection fraction (HFpEF) in the setting of obesity without concomitant type 2 DM, documenting the superiority of this drug in a wide population of individuals with metabolic co-morbidities and related complications.

Semaglutide appears to be one of the most effectiveGLP-1 receptor agonists concerning body weight reduction and achievement of normoglycemia; its use, compared to other currently prescribed GLP-1 receptor agonists, has been associated with significantly higher odds for achieving optimal glycated hemoglobin levels body weight reduction greater than 5% and 10%, compared to baseline, at the cost of higher odds for adverse gastrointestinal events [13]. However, those gastrointestinal adverse events are, mostly, transient, mild and manageable with symptomatic therapy, resulting in very low discontinuation rates [13]. Of course, it has to be highlighted that treatment with GLP-1 receptor agonists has also been shown to significantly increase the risk for gallbladder and biliary diseases, mainly cholelithiasis and cholecystitis, however, no significant increase in the risk for pancreatitis (acute or chronic) or pancreatic cancer has been documented [14].

1.2. The potential therapeutic role of semaglutide for PLWH

Thus, the question that arises is whether semaglutide could prove as a safe and highly efficacious treatment option for PLWH with metabolic co-morbidities, as in the general population. A recently published observational study from the United States utilizing data from the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort, in a total of 222 PLWH using semaglutide with a mean follow-up period of 1.1 year, demonstrated that treatment with semaglutide, titrated up to a maximum dose of 1.0 mg once-weekly (as 77% of enrolled participants had concomitant type 2 DM), was associated with an average weight loss of 6.5 kilograms (kg), compared to baseline, along with a significant reduction in glycated hemoglobin levels by 1.07% [15]. Overall safety and efficacy profile of semaglutide was similar to that observed in the general population, with no important differences; of course, it should be noted that the study enrolled PLWH, of whom 97% were on ART and 89% were virally suppressed, with a mean body mass index (BMI) of 35.5 kg/m^2 and a 77% prevalence of type 2 DM in the overall cohort [15]. Thus, indeed, the baseline characteristics of PLWH within this cohort were not substantially different from those observed in a typical cohort retrieved from the general population. It has to be noted that most adverse events were mild gastrointestinal symptoms, without any reported cases of gallbladder, biliary, or pancreatic disorders.

Important insights were provided by a recently published phase 2b randomized controlled trial (RCT) from a single site in the United States, which enrolled 108 PLWH and HIV-associated lipohypertrophy, and were randomly assigned to semaglutide 1.0 mg or placebo for 32 weeks [16]. Treatment with semaglutide 1.0 mg once-weekly versus placebo resulted in significant decreases in body weight by 10.4%, BMI by 11.2% and waist circumference by 8.3%, compared to baseline [16]. In addition, semaglutide provided significant reductions in total body fat by 18.9%, in total limb fat by 17.3% and in trunk fat by 21.6% [16]. Last, but not least, semaglutide compared to placebo induced significant reductions in abdominal total adipose tissue by 15.1%, in abdominal subcutaneous adipose tissue by 11.2% and in abdominal visceral adipose tissue by 30.6% [14]. Of note, a significant improvement in several other cardio-metabolic risk markers (glucose metabolism, lipid profile, blood pressure) was shown, whereas 4 PLWH receiving semaglutide (7%) developed during study an adverse event requiring premature treatment discontinuation [16]. However, there was no documented difference in the risk for possibly related or related adverse events between semaglutide and placebo, confirming a safety profile similar to that observed in the general population [16]. Again, in this trial, most adverse events observed with semaglutide were grade 1 gastrointestinal symptoms, while two cases of cholelithiasis and one case of elevated lipase levels related to semaglutide treatment were reported.

Ultimately, another recently published, phase 2b, open-label trial, the SLIM LIVER study, enrolling 49 PLWH and MASLD, documented that 24-week treatment with semaglutide 1.0 mg once-weekly resulted in a mean reduction in intrahepatic triglyceride, as a marker of liver fat assessed by magnetic resonance imaging-proton density fat fraction, by 31.3% [17]. Indeed, 29% of enrolled PLWH achieved complete resolution of MASLD, whereas 58% had a reduction in intrahepatic triglyceride levels by at least 30% [17]. Of note, treatment with semaglutide resulted in a mean reduction in BMI by 8.1%, in body weight by 8.1% and in waist circumference by 5.8%, along with a significant reduction in fasting plasma glucose, glycated hemoglobin, and fasting triglyceride levels [17]. Semaglutide was well tolerated, while most reported adverse events were mild gastrointestinal symptoms, not resulting in treatment discontinuation [17]. No cases of gallbladder, biliary, or pancreatic adverse events were reported in this study.

It has to be noted that in none of the above-mentioned studies [15–17] was reported any side effect stemming from a drug–drug interaction between semaglutide and background ART. In addition, concomitant ART was not found to increase the risk for adverse side effects with semaglutide treatment. To date, there is no relevant evidence of such an interaction, although larger studies with longer follow-up periods are required, to answer this important safety issue.

Concerning the two trials by Eckard et al. [16] and Lake et al. [17], it has to be highlighted that at the time of study design and initiation, the maximum approved dose of semaglutide by the FDA was 1.0 mg once-weekly, while, later, the FDA approved semaglutide 2.4 mg once-weekly for the management of overweight/obesity without concomitant type 2 DM.

Finally, it has to be highlighted that none of the above-mentioned studies performed in PLWH [15–17] have assessed the effect of semaglutide on lean body mass, while it has been shown that GLP-1 receptor agonists, indeed, decrease lean body mass. Recent evidence suggests that from the total weight lost with semaglutide treatment, 61% derives from loss in fat mass and 39% from loss in free fat mass [18]. Therefore, treatment with GLP-1 receptor agonists should be initiated with caution in individuals with sarcopenic obesity. Of note, in a recently published, secondary analysis from the SLIM-LIVER study, treatment with semaglutide among PLWH resulted in a significant reduction in psoas muscle volume by 9.3%, without any significant change in psoas muscle fat [19]. In addition, no significant difference in physical function was demonstrated after semaglutide treatment in that population [19]. However, the data are preliminary and further studies are warranted in order to shed light on this important issue both in the general population and in PLWH.

1.3. Expert opinion

Cardio-metabolic burden among PLWH is constantly increasing, resulting in increased morbidity and mortality in an era of very high adoption and success rates, in terms of viral suppression, of ART. Prevalence of cardio-metabolic disease among PLWH appears to be similar to that observed in the general population; increased lifespan achieved with ART, along with modern lifestyle, especially in the developed countries, has resulted in a significant increase in the prevalence of cardio-metabolic co-morbidities in that population, which deserve our attention. Therefore, there is an urgent need for specific treatment recommendations in this population, to mitigate those risks and decrease overall morbidity and mortality. Of course, we also need relevant evidence across important safety issues, based on the specific ART regimens utilized in that population, which have resulted in significant increases in life expectancy for PLWH, but are also associated with higher risk for the development of metabolic co-morbidities.

Semaglutide is probably the most prominentGLP-1 receptor agonist to date, with established efficacy in terms of glycemic control and significant body weight reduction, along with impressive cardio-renal benefits in individuals with type 2 DM, obesity, or both. It seems that semaglutide is one of the 'key players' for the treatment of cardio-kidney-metabolic syndrome, although its high cost and supply shortages have been, so far, the main barriers to its widespread adoption. Notably, the use of semaglutide has been associated with substantial and durable body weight reduction, exceeding 15%, and improved glucose control, which further translates into type 2 DM prevention, possible disease remission, and improvement of cardiometabolic risk factors and associated complications, giving hope to patients of a longer and healthier life.

Preliminary evidence from studies enrolling PLWH suggests that semaglutide is highly efficacious in this population, with a safety profile similar to that documented in the general population. Those studies suggest significant reductions in body weight and BMI, blood glucose, total body fat, liver fat, abdominal subcutaneous and visceral adipose tissue, showing a significant shift toward 'healthier' anthropometric characteristics and metabolic indices among PLWH.

Semaglutide may potentially become a groundbreaking treatment solution for PLWH suffering from metabolic co-morbidities; however, we need larger, well-designed, dedicated RCTs, with emphasis on both safety and efficacy, and relevant cost-effectiveness analyses, to inform clinical decision-making for this specific population.

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Author contributions

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