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Semaglutide-eye-catching results

Cigrovski Berkovic M *et al*. Semaglutide and retinopathy

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INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1RA) are a class of drugs increasingly used for the treatment of patients with type 2 diabetes mellitus (T2DM), enhancing glucose management while promoting weight loss and exposing patients to no significant hypoglycemic risk[1]. In addition to the abovementioned advantages, most agents within the class also provide cardiovascular benefits to diabetic patients, who are well known to be at high risk for cardiovascular atherosclerotic disease. Specifically, seven dedicated cardiovascular outcome trials (CVOTs), *i.e.*, LEADER, SUSTAIN-6, EXSCEL, HARMONY, REWIND, ELIXA, and PIONEER-6, included patients on liraglutide, once weekly sc semaglutide, exenatide, albiglutide, dulaglutide, lixisenatide, and daily oral semaglutide respectively. Data obtained from those CVOTs suggested benefits for T2DM patients with a longstanding history of diabetes, obesity, or overweight in terms of primary and secondary prevention of adverse cardiovascular (CV) events for liraglutide, semaglutide, albiglutide, and dulaglutide, while neutrality was proven in the ELIXA trial[2-8]. Other benefits were also noticed, including reduced albuminuria and improved kidney function in terms of hindered diabetic nephropathy progression and lower need

for kidney replacement therapy[9]. However, conflicting data were reported concerning another relevant microvascular complication, *i.e.*, diabetic retinopathy (DR)[10].

DR-PATHOPHYSIOLOGY

DR is the main microvascular complication of diabetes, currently affecting approximately 100 million people worldwide. It increases the likelihood of visual impairment and blindness by 64% and 27%, respectively. Data from the US suggests that almost a third of patients with diabetes over 40 years of age have DR[11,12]. According to the meta-analysis performed for patients with type 1 diabetes, the long-term risk of developing DR can be reduced by intensive glucose control, granting the achievement of near-normal glucose levels[13]. Despite United Kingdom Prospective Diabetes Study results showing that each 1% reduction in HbA1c was associated with a 37% reduction in the development of retinopathy in patients with T2DM[14], conflicting results were also reported concerning the association of tight glucose control with the worsening of previously identified DR signs[15]. However, along with persistent hyperglycemia, risk factors for DR onset include the patient's age, diabetes duration, and high blood pressure, together with genetic predisposition, smoking habits, anemia, non-Caucasian ethnicity, and hyperlipidemia[16-19]. Indeed, pre-existing DR progression can also be related to the magnitude of HbA1c reduction, where data support the evidence of temporary, paradoxical DR worsening during the first three to 36 mo of initiation of intensive glucose lowering before the long-term benefits of glucose optimization become apparent[13,20,21]. The abovementioned deterioration in DR has been described in patients with T1DM and T2DM and during pregnancy. It was initially noticed in patients intensively treated with continuous subcutaneous insulin infusion, but afterward with various diabetic pharmacotherapy, as well as bariatric surgery and pancreatic transplantation[22].

The pathophysiology of DR includes persistent hyperglycemia-related retinal microvessel dilatation, abnormal permeability, and ischemic occlusion with subsequent neovascularization resulting from up-regulation of vascular endothelial growth factor (VEGF) expression[14,23-25]. The evidence available from *in vivo* and *in vitro* models

suggests a significant role of longstanding and generalized low-grade chronic inflammation inducing neurodegeneration and oxidative stress at the retinal level[26-29]. Also, according to Zhou *et al*[30], visual function maintenance requires special attention to any available methods, including GLP-1 analogs, to protect retinal ganglion cells from their high intrinsic vulnerability to any sources of damage.

In addition, what is often forgotten is that the metabolic memory, widely recognized as a significant factor in diabetes complications onset and progression, involves the whole body, including the eye, where it acts by increasing the cytosolic protein Drp1 translocation inside the mitochondria with enhanced GTPase activity in response to various stimuli, including hyperglycemia[31,32]. Such changes consistently impair mitochondrial dynamics even after getting back to normoglycemia. Because of that, retinal capillary cells undergo accelerated apoptosis due to cytochrome C leakage into the cytosol due to functional and structural mitochondrial changes, including the DNA. This phenomenon impairs perfusion of acellular capillaries with subsequent neovascularization[33,34].

THEORIES EXPLAINING EARLY WORSENING OF DR

Although various theories exist trying to explain changes in retinal blood flow and hemodynamics associated with early worsening of DR, the mechanism has not been fully elucidated, while optimal *in vitro* conditions and animal models are still lacking[35]. For example, the osmotic theory suggests blood glucose changes to alter lens hydration through altered osmotic pressure, thus causing hyperopic/myopic changes[36,37]. Indeed, insulin has been mostly associated with early DR worsening so far. The mechanisms behind that phenomenon seem to be blood-retinal barrier disruption in the presence of hyperglycemia, consequent to microvascular changes induced by enhanced VEGF production and expression through increased endothelial cell reactive oxygen species (ROS) concentrations, and the often associated hypoglycemic events, which also trigger oxidative stress thus further building up ROS concentrations over time[35,38-40]. In addition, persistently increased IGF-1 levels accompanying fast-improved glucose

control might also have a role in initiating or worsening DR[41]. The classification and reporting of this phenomenon are further complicated by the highly variable definition of "DR worsening" by different authors, including cotton-wool exudates, hemorrhages, microaneurysms, intraretinal microvascular abnormalities, and capillary-free areas[42]. Nonetheless, we feel reassured enough by some reports concerning improved DR in the follow-up of patients maintaining tight glucose control over time[43].

GLP-1RA EFFICACY IN GLUCOSE LOWERING AND VASCULAR EFFECTS

As already pointed out, among GLP-1RAs, semaglutide, dulaglutide, and liraglutide proved to prevent major cardiovascular events in the large CVOTs published so far[44]. However, the mechanism behind this observation is still unclear but might include the already mentioned antihyperglycemic and weight loss effects, the potential to decrease systolic and diastolic blood pressure, and more direct endothelial protective mechanisms[45]. In addition to that, GLP-1RAs offer benefits in terms of lowering unfavorable renal outcomes[9]. Such relevant effects also depend on their ability to rapidly and consistently grant quite good glycemic control with significant reductions in HbA1c levels[46]. Their effect on DR is poorly understood and somewhat conflicting, as experimental data even suggests for GLP-1RAs protective effects through hindered blood-retinal barrier disruption and retinal neuron apoptosis[47].

On the other hand, one of the published retrospective studies with exenatide showed a significant proportion of treated patients with fast-improved HbA1c to be at risk of development and progression of DR, in addition to other potentially identified risk factors such as duration of diabetes and presence of preexistent DR[48]. However, the follow-up study published by the same authors reported improved DR in 62% of patients, with no documented DR status changes in a further 18% of patients and DR progression in the remaining 20% (n = 8). Moreover, maculopathy verified in the initial study either regressed or kept stable. In the case of patients with new-onset DR occurring after exenatide initiation, there was evidence of some improvement in 71% (n = 10), and stabilization in three more patients (21%)[49]. An additional interventional case study with

exenatide showed complete regression of diabetes-related macular edema and improved visual acuity within one month[50]. On the other hand, multivariate analysis in the AngioSafe study, which included a cohort of 3154 patients with T2DM, found no association between the exposure to GLP-1RAs (liraglutide and exendin-4) and severe DR ($P = 0.47$)[51]. Similarly, cohort studies from registries did not show any additional risk of DR complications with GLP-1RAs as compared to oral incretin therapy with dipeptidyl peptidase-4 (DPP-4) inhibitors[52], while the results of Brooks and Lissett's investigation suggested a dramatic deterioration of DR be associated with significantly improved HbA1c levels achieved within four months of exenatide treatment[53].

Further on, the LEADER, SUSTAIN-6, and REWIND CVOTs, including liraglutide, subcutaneous semaglutide, and dulaglutide and having retinopathy as a secondary outcome measure (quite broadly pre-specified as vitreous hemorrhage, diabetes-related blindness defined as Snellen visual acuity equal or less than 20/200 or a visual field lower than 20 degrees, or requirement for retinal photocoagulation, intra-vitreal anti- VEGF treatment, or vitrectomy) reported no decrease in DR rate[3,4,7]. Instead, DR complications tended to increase in LEADER and REWIND [hazard ratios 1.15 (95%CI: 0.87-1.52) and 1.24 (95%CI: 0.92-1.68), and significantly increased in the SUSTAIN-6 trial [50 events/1648 people in the semaglutide group *vs* 29 events/1649 people in the placebo group; hazard ratio 1.76 (95%CI: 1.11-2.78)]. In the meta-analysis by Bethel and coauthors[54] including patients treated with semaglutide (oral and subcutaneous), dulaglutide, exenatide, and albiglutide, with similar age (range 62-66 years), and BMI (32-33 kg/m^2), 31%-46% were women, and the mean duration of diabetes ranged from 10 to 15 years. Mean HbA1c ranged from 7.3% to 8.7% (56.3-71.6 mmol/mol), and previous CVD was established in all patients included in the HARMONY trial (albiglutide), while 70% of patients in the REWIND trial (dulaglutide) only had CV risk factors. The prevalence of a differently defined among trials DR ranged from 9.0% to 28.2% at baseline in the REWIND, HARMONY, and PIONEER-6 trials. Moreover, PIONEER-6 excluded patients with already established DR, while only SUSTAIN-6 and PIONEER-6 evaluated retinopathy outcomes with fundus photography or fundoscopy as a scheduled study

protocol. The authors did not report a significant association between DR risk and overall GLP-1RA use. However, the data suggested higher differences in the HbA1c levels during the first three months of GLP-1RA initiation in SUSTAIN-6 to represent the most significant risk for DR, while trials EXSCEL, HARMONY, and PIONEER-6, which were associated with negligible impact on HbA1c during the first three months of treatment initiation, did not point out any significant DR risk. Moreover, in line with other evidence, DR risk was not related to blood pressure or weight changes[55]. So, the most critical limitation in DR retinopathy data interpretation is the non-homogeneity of all GLP-1RAs CVOTs in the method of adjudication of DR events and the assessment of DR through widely used scores[10,56,57].

IS SEMAGLUTIDE TO BLAME?

Semaglutide had an extensive efficacy and safety program (SUSTAIN). In studies SUSTAIN 1-5 and SUSTAIN 7, the DR status was annotated within the medical history as not present, present, or unknown, and if present, designated as proliferative, nonproliferative, or unknown and considered an adverse event; patients with proliferative DR and maculopathy requiring acute treatment or HbA1c > 10% and > 10.5%, respectively, did not enter the study. In the SUSTAIN-6, instead, patient exclusion criteria did not take into consideration upper HbA1c limits or the presence of DR, which was indeed adjudicated as a composite endpoint as already described[58,59]. When compared to the overall SUSTAIN-6 study population, those patients developing eye complications had the more severe disease as defined by longer diabetes duration (17.5 years *vs* 13.9 years), higher initial HbA1c (9.4% *vs* 8.7%), and higher insulin-treatment rate (75.9% *vs* 58.0%). Moreover, those patients had a higher proportion of more advanced DR complications at baseline and achieved a more relevant HbA1c reduction during the first 16 wk of semaglutide treatment[58].

On the other hand, a recent meta-analysis of GLP-1RA CVOTs failed to find any association between the drug class with retinopathy. However, after stressing that the abovementioned trials had a median follow-up of 3.4 years (*i.e.*, much shorter than

needed for retinopathy onset), used different diagnostic criteria, and were not even powered enough to assess the incidence of retinopathy, the authors reported on a significant association of such complication with HbA1c downward slope (*i.e.*, 0.77, $P < 0.01$), quantifiable as a 6%, 14%, or 8% increased Ln (OR) at 3-mo, 1-year, and overall follow-up, respectively, every 0.1% (1.09 mmol/mol) increase in HbA1c reduction[54].

On the whole, according to a post hoc analysis, the degree of HbA1c decrease and pre-existing retinopathy stood out as the main retinopathy worsening factors[58], yet SUSTAIN-7, *i.e.*, a head-to-head dulaglutide-semaglutide comparison study, showed DR onset or worsening in only two patients (1%) on semaglutide 0.5 mg, two (1%) on dulaglutide 0.75 mg, two (1%) on semaglutide 1.0 mg, and three (1%) on dulaglutide 1.5 mg[59]. Indeed, as no one expects any drugs to develop advanced DR signs in such a short period as the one provided by SUSTAIN-6, a randomization bias might have occurred regarding DR severity assessment at study entry due to the focus on cardiovascular disease monitoring. Once again, the above consideration and the dramatic drop in blood glucose levels might better explain DR results[60].

DATA FROM OBESITY TRIALS INVOLVING GLP-1RAS

Contrary to what we reported above, when turning to GLP1-RAs utilization in obesity, retinopathy was not reported as a complication in long-duration trials assessing weekly semaglutide 2.4 mg injection *vs* placebo for weight loss in obese patients[61-63] and, based on a recent revision of the literature, no definite conclusions can be drawn on the role of semaglutide in the incidence or worsening of retinopathy[64], especially when taking into account a systematic review and meta-analysis of all trials, which ruled out any increased DR risk compared to placebo (RR: 1.14, 95%CI: 0.98-1.33), despite suggesting caution in the case of older patients with the long-standing disease (age ≥ 60 years and diabetes duration ≥ 10 years) due to a higher DR risk (RR: 1.27, 95%CI: 1.02-1.59; RR: 1.28, 95%CI: 1.04-1.58, respectively)[65].

EXPERIMENTAL DATA ON MECHANISMS UNDERLYING THE GLP-1RAS/RETINOPATHY ASSOCIATION

The Consortium for the Early Treatment of DR (EUROCONDOR) study failed to find any signs of neurodegeneration in a significant percentage of patients with microangiopathic retinal lesions[66,67]. However, as already mentioned before, neurodegeneration has been proposed as a hallmark of DR[68-70]. Indeed, the American Diabetes Association (ADA) has classified DR as a microvascular and neurovascular complication[29]. In Figure 1 we present the schematics of development of DR. So, at present, drugs like GLP-1RAs, expected to protect both neurons and microvessels, are suggested for the management of early DR stages[71,72].

In such a perspective, a protocol recently set up to rule out a direct role of the drug in retinal damage evaluated the effect of a semaglutide eye-drop solution on retinal neurodegeneration, neuroinflammation, and early vascular leakage in mice. Study results suggested that the drug prevents exactly those three features of diabetes-related retinal damage. The mechanism behind this phenomenon seemed to rely on the decisive anti-inflammatory action linked to decreased expression of NF-kB, proinflammatory cytokines (IL-1, IL-6, and IL-18), and ICAM-1, as well as on the prevention of neuroretinal cell apoptosis promoted by the activation of Akt pathway, which is essential for neuron survival[70]. Moreover, as blood glucose levels were not affected by topical administration, no confounding factors were present due to eventually occurring drops in glucose concentrations. Interestingly, recent results from mice experiments also suggested that semaglutide is unable to cross the blood-brain barrier[73] and has beneficial rather than deleterious effects, as already reported with other GLP-1RAs in the experimental animals[71,72,74,75], possibly due to improved blood-retina barrier function and neuronal apoptosis[47], reduced glutamate levels obtained through upregulated glutamate-aspartate transporter (GLAST)[75], and decreased placental growth factor and intercellular adhesion molecule-1 expression[71,72].

THE FUTURE OF SEMAGLUTIDE REGARDING RETINOPATHY

The potential direct mechanism of action of GLP-1RA on the retinal cells is still elusive and debated. Although the GLP-1 receptor is present in the human eye, no GLP-1R expression was found in the eyes of people with long-standing proliferative DR[76].

However, the effects of a newly identified confounding factor, *i.e.*, subtle differences in individual gut microbiota composition, cannot be easily ruled out. Indeed, despite the relationship between intestinal microbiota and host still requiring complete elucidation, gut dysbiosis, *i.e.*, the chronic disequilibrium within the many different microbial colonies, seems associated with several inflammatory/metabolic diseases and central nervous system disorders, including retinopathy as an expression of the emerging concept of the so-called "microbiota-retina axis". Indeed, as longstanding diabetes is associated not only with retinopathy but also with significant intestinal dysbiosis[77,78], relevant changes in the bacterial population might trigger the onset of retinopathy *via* their influence on the lipid content of both retinal and CNS tissues, eventually responsible for decreased intraocular succinate concentrations or increased trimethylamine-N-oxide (TMAO) plasma levels[79-86].

Retinopathy is a disabling disease, so rehabilitation should start as soon as possible when prevention fails. Based on the abovementioned neuroinflammatory mechanisms, several anti-inflammatory substances may help prevent DR progression, including nutritional supplements like resveratrol. However, the latter, despite looking promising enough, has a too low level of bioavailability and is contraindicated in the frequently occurring case of iron-deficiency-dependent anemia[87].

DETAILS CONCERNING SEMAGLUTIDE'S PHARMACOLOGIC PROPERTIES FAVORING DR SAFETY

Semaglutide has a 94% amino acid sequence homology to native GLP-1. However, structural modifications from endogenous GLP-1, *i.e.*, alanine residue substitution at the 8th position with Aib, make it less susceptible to degradation by DPP-4 while acylation of Lysine residue at the 26th position and attachment of a C18 fatty-diacid increase its binding affinity to albumin. The above changes result in a half-life of approximately one

week, making it appropriate for once-weekly use in clinical practice. In the phase-3 SUSTAIN trials semaglutide showed superiority to different comparators and during different stages of diabetes in reducing HbA1c and body weight. In a SUSTAIN-6 trial investigating cardiovascular outcomes, semaglutide led to a 26% reduction in risk of the primary 3-point MACE (a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) when compared to placebo. The pharmacokinetic properties of semaglutide are not significantly affected by impaired hepatic or renal function. Therefore, no dose adjustments are required in that case. It achieves a steady state concentration in 4 wk to 5 wk (both subcutaneous and oral form). Indeed, in the case of subcutaneous semaglutide, 1 d to 3 d are needed to achieve the maximum concentration, and, in the case of oral semaglutide, one hour is needed following intake. Moreover, during clinical pharmacology studies, no relevant impact of semaglutide on concomitant orally administered medications was observed, making its use safe in a broad population[88]. Semaglutide improves the efficiency of incretin function by activating GLP-1 receptors and enhancing GLP-1 to supraphysiological levels. It reduces fasting and postprandial glucose levels by promoting insulin secretion in a glucose-dependent manner and suppressing hepatic gluconeogenesis through blunted glucagon release. Moreover, it improves both proinsulin to insulin ratio, which suggests improved β-cell function and insulin sensitivity through body weight and fat loss consequent to reduced energy intake and gastric motility[89].

A cardiovascular risk (3-P MACE) reduction effect compared to placebo was shown for injectable and oral semaglutide in SUSTAIN-6 and PIONEER-6 trials, respectively. Animal studies have shown antiatherosclerotic effects mediated by regulating multiple inflammatory pathways and antiapoptotic effects in cardiac cells[90]. In addition, three ongoing trials, *i.e.*, SOUL (NCT03914326), SELECT (Semaglutide Effects on Heart Disease and Stroke in Patients with Overweight or Obesity; NCT03574597), and STRIDE (NCT04560998), will give further insight into different cardiovascular effects of both oral and subcutaneous semaglutide in patients with and without T2DM, and overweight/obesity[91-93].

The semaglutide mechanism of action is glucose-dependent and, therefore, associated per se with a shallow risk of hypoglycemia. Nevertheless, semaglutide cannot avoid the risk of hypoglycemia due to add-on sulfonylureas or insulin. Such drug association might initially cause acute glucose level drops and probably transient worsening of DR, as observed in the first four weeks of treatment[58].

CONCLUSION

Nowadays, the most robust relationship between semaglutide treatment and early worsening of DR might find its sizable initial impact on HbA1c as a suitable explanation. Indeed, both semaglutide formulations (subcutaneous and oral) have been investigated in two phase-3 clinical programs, *i.e.*, the SUSTAIN and PIONEER program. Combining all individual studies within these two programs, over 21500 patients participated in the studies with a treatment duration of at least 26 wk, giving a plethora of safety evidence[94]. Data insinuating a connection between semaglutide and DR emerged during the phase-3 trials. However, the answer to whether that phenomenon depended on the drug itself or the magnitude of fast-occurring glucose lowering will come from the presently underway FOCUS trial on approximately 1500 patients with T2DM, a bilateral 10 to 75 Early Treatment DR Study (ETDRS) score and no need for ophthalmologic therapy. Such a study will analyze once-weekly subcutaneous semaglutide 1.0 mg compared with placebo for up to 5 years, with the primary endpoint of at least three-digit ETDRS score progression[95]. Until FOCUS results become available, caution is mandatory in patients with DR. It may be wise to perform fundoscopy prior to semaglutide therapy, and existing DR should be treated concomitantly. In addition, given the strong effects of semaglutide on glucose levels, down-titrating basal insulin therapy or stopping sulphonylurea will prevent rapid decreases in glucose concentrations, thereby reducing the risk of acute DR worsening. Guidelines on DR management do not differ for patients receiving other antidiabetic agents. Therefore, the same treatment, including anti-VEGF agents, should be applied.

Both current and future research on GLP-1RA is quite exciting and targets different metabolic conditions and health aspects associated with both T2DM and obesity, such as cognitive health and dementia, PCO, and NAFLD.

However, the scientific community must shed light on the topic and draw definite conclusions concerning a direct mechanism of one (or more) GLP-1RA class drug(s) in retinopathy development and worsening.

Care required by T2DM patients initiating GLP-1RA treatment does not differ from that expected with other types of intensive glucose-lowering medication, *i.e.*, early detection of DR onset/progression and, eventually, specific treatment. Screening for DR is recommended for patients at the time of T2DM diagnosis and then annually while also taking into account individual metabolic control and baseline DR conditions[96]. In the case of severe, proliferative DR, treatment of retinopathy should start before or with intensive glucose-lowering therapy, expecting a typically transient worsening though[97]. While increasingly more overweight and obese T2DM patients at high CV risk start on GLP-1RAs, clinicians should consider their DR status upon initiation and adopt the best available treatment for DR when present.

When choosing semaglutide in the intensification of T2DM treatment, a cautious attitude is mandatory, at the moment, especially in the case of coexisting insulin treatment and advanced disease stages.

Figure 1 Main mechanisms involved in blood vessels injury and neuroinflammation in the diabetic retina. VEGF: Vascular endothelial growth factor.

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