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COMMENT

Semaglutide and the risk of diabetic retinopathy—current perspective

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Semaglutide (Novo Nordisk, Bagsvaerd, Denmark) is a potent glucagon-like peptide 1 (GLP-1) analogue with a high degree of homology to human GLP-1. Semaglutide once weekly subcutaneous dose (Wegovy®) has recently received approval by the United States Food and Drug Administration (US-FDA) for its use in chronic weight management. Semaglutide is indicated for chronic weight management in adults with a body mass index (BMI) of 27 kg/m^2 or greater who have at least one weight-related comorbidity such as type 2 diabetes (T2D) or hypertension, or in adults with a BMI of at least 30 kg/m^2 [1]. This is being considered as a game changer in this area and is likely to be used more frequently than ever before. US-FDA has three labelled approvals for semaglutide in total. First, subcutaneous injection once-weekly (Ozempic®) [2], second oral administration once-daily (Rybelsus®) [3] both are indicated as an adjunct to diet and exercise to improve glycaemic control in adults with T2D mellitus. Third indication is once weekly subcutaneous dose (Wegovy®) for chronic weight management as described above.

Two large phase 3a pre-approval Cardiovascular Outcome Trials, Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) 6 [4] and PIONEER 6 [5], investigated the effects of subcutaneous and oral semaglutide versus placebo on Major Adverse Cardiovascular Events (MACE) in patients with T2D and high cardiovascular (CV) risk. The primary endpoint was time from randomisation to first occurrence of an adjudicated 3-component composite MACE endpoint defined as CV death, non-fatal myocardial infarction, or non-fatal stroke. The SUSTAIN 6 trial demonstrated a higher incidence of diabetic retinopathy (DR) in the intervention arm [4]. Despite patients with proliferative DR being excluded from PIONEER 6, a 0.8% increase in DR was observed with oral semaglutide [5].

We expect that after the FDA approval of this drug in weight reduction and Novo Nordisk's aggressive stance to introduce the oral formulation for all indications, use of this drug will significantly increase. Hence, it is important to bring to the attention of ophthalmologists the background of its data from SUSTAIN 6 and the FOCUS trial [4, 6].

SUSTAIN 6

The SUSTAIN trials 1–6 and two Japanese trials have studied the efficacy and safety of semaglutide [4, 7–11].

There were a few significant differences between the SUSTAIN 6 and SUSTAIN 1–5 and the Japanese trials. In the latter, the upper limit of HbA1c was fixed at 10 or 10.5% and proliferative retinopathy or maculopathy requiring immediate therapy were excluded. On the contrary, SUSTAIN 6 had neither any inclusion/exclusion criteria related to DR, nor a HbA1c cut-off and as a matter of fact the secondary outcome measures in the SUSTAIN 6 trial included assessment of DR complications as part of microvascular complication analysis. Diabetes-related blindness was defined as Snellen visual acuity of 20/200 [6/60] or less, or a visual field of 20 degrees or less, in the better eye with the best correction possible at the time of the event. Need for retinal photocoagulation and intravitreal agents were part of outcomes. Furthermore, incidence of vitreous haemorrhage was assessed.

The Japanese trials and the SUSTAIN 1–5 had 3.7–14.5% of patients with DR at baseline whereas, SUSTAIN 6 had 29.4% of patients with DR at baseline (semaglutide, 30.9%; placebo, 27.8%). The number of patients with proliferative DR at baseline were similar in both the treatment groups (semaglutide, 6.3%; placebo, 6.0%)

In SUSTAIN 6 trial, the development of retinopathy related complications were significantly higher in the semaglutide group, occurring in 50 (3%) vs. 29 (1.8%) patients of the placebo group. (HR = 1.76; 95% CI, 1.11–2.78; $P = 0.02$). 16 (1%) patients developed vitreous haemorrhage in semaglutide group when compared to only 7 (0.4%) patients in the placebo group and 5 (0.3%) patients developed diabetes-related blindness in the semaglutide group when compared to 1 (0.1%) patient in the placebo group. These complications warranted the necessity of retinal photocoagulation in 38 patients (2.3%) in the semaglutide group vs. 20 (1.2%) in the placebo group. 16 (1%) patients required Intravitreal injections in the semaglutide vs. 13 (0.8%) patients in the placebo group.

On comparative analysis of the data of SUSTAIN 6 with the complete SUSTAIN trial programme, it is apparent that the 79 patients who suffered a retinopathy complication had a longer duration of diabetes and higher mean HbA1c, 9.4% for the retinopathy group vs. 8.7% in the complete group. 65% of the retinopathy groups were taking insulin compared to 58% of the overall population. 83.5% of participants had a history of DR at baseline. Proliferative retinopathy was observed in 29% of patients

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in the complications group vs. 6.1% of the participants overall and laser or injection therapy for proliferative retinopathy was needed in 17.7% vs. 3.4% respectively.

The risk of DR was low for semaglutide-treated patients with no known pre-existing DR at baseline. 5 patients [10.0%] with no pre-existing DR at baseline developed an event in the semaglutide group and 4 [13.8%] in the placebo group. Overall, a higher risk for DR complications were observed with semaglutide in patients with proliferative and non-proliferative DR at baseline.

From the above analysis it is evident that SUSTAIN 6 had worse baseline characteristics such as high HbA1c, more patients on insulin, more patients with advance retinopathy and patients who needed laser or injection which might be the cause of the results showing further progression of DR and its complications. However, baseline characteristics were similar for the placebo group also which did not show such progression. The reduction in HbA1c with semaglutide versus placebo in patients with DR complications was 1.9% and 2.5% at week 16 with semaglutide 0.5 and 1.0 mg respectively, whereas it was 0.9% and 1.3% with placebo 0.5 and 1.0 mg. Hence, a more reasonable scientific explanation is that semaglutide caused faster HbA1c reduction compared to placebo which could have caused the worsening of DR in the first 16 weeks. It has been established since the time of Diabetes Control and Complications Trial (DCCT) [12] and UK Prospective Diabetes Study (UKPDS 33) [13] that marked reductions in HbA1c, as a result of improved glycaemic control is associated with transitory worsening of DR.

FOCUS TRIAL

In spite of the explanation that worsening of DR could be due to the rapid lowering of blood glucose, it is important to establish it with a long-term trial focused on eye. Hence, a dedicated ophthalmic trial (FOCUS) of 5 years treatment duration that will assess the long-term effect of semaglutide on DR development and progression is initiated by Novo Nordisk. Results of the FOCUS trial are expected in 2026 [6].

To summarise, until we get level 1 evidence from FOCUS trial, it is recommended for physicians to ensure patients are screened for DR before initiating semaglutide and on the basis of the stage of retinopathy, physicians and retina specialists need to discuss the risk benefit ratio in initiating the treatment.

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ADDITIONAL INFORMATION

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