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Semaglutide (Ozempic®, Wegovy®) and its effect on diabetic retinopathy

Semaglutide (Ozempic, Wegovy) is an injectable glucagon-like peptide-1 (GLP-1) analogue that is approved for the treatment of type 2 diabetes (T2D) and obesity.[1] It works by slowing gastric emptying and reducing glucose absorption to reduce serum glucose levels.[1] This class of medication has gained significant traction over the past few years due to its significant and sustained improvements in glycated hemoglobin (HbA1c) and body weight vs placebo. In the SUSTAIN-6 trial, semaglutide showed a statistically significant 26% risk reduction in major adverse cardiovascular events when compared to placebo, along with an average weight loss of 10.8 pounds and lower average A1c by 1%.[2] These outcomes have made GLP-1 analogues a preferred agent for treatment of patients with diabetes[1], and the drugs have even become popularized as a weight loss drug by celebrities in mainstream media. However, despite its clear benefits, semaglutide has also been linked to an increased incidence of diabetic retinopathy (DR).

The SUSTAIN clinical trial program evaluated the efficacy and safety of semaglutide prior to its FDA approval. During these trials, semaglutide was found to be associated with a significant increase in the risk of diabetic retinopathy (DR) complications vs placebo despite overall improvements in incidents of cardiovascular events and renal complications at the 2 year point.[2] Post publication analysis showed that patients who developed diabetic retinopathy complications were characterized by a longer mean diabetes duration, higher mean HbA1c levels at baseline, and greater likelihood to have been receiving insulin treatment at trial entry.[3] Furthermore, there was a statistically significant higher risk for DR complications with semaglutide in patients with proliferative and non-proliferative DR at baseline.

The authors felt that much of the DR effect with semaglutide vs placebo was attributable to the magnitude and rapidity of HbA1c reduction during the first 16 weeks of treatment in patients,3 and was balanced out by the benefits of long term glucose control.

This paradoxical worsening of DR after a sudden drop in blood glucose is a well-documented phenomenon. The landmark DCCT (Diabetes Control and Complications Trial) found an association between better blood glucose control and risk of early worsening of DR.[4] Another study looked at patients after intensive insulin treatment, pancreas transplant, or bariatric surgery, and found that 10% to 20% of patients had worsening of DR within three to six months—with twice that much for patients who already had advanced DR at baseline.[5]

The data shows that there is a real risk of DR progression with the use of semaglutide, but should we as ophthalmologists be concerned? And how should we be addressing this with our endocrinology and primary care physician colleagues?

Consensus in the retina community is that progression of DR is not a reason to keep the patients off these very effective medications.[6] Whether patients progress in diabetic retinopathy or not, the advantages of overall reduction of cardiovascular disease should likely take priority. Additionally, many of these patients may have intermittent worsening of retinopathy for the first year or two, but often develop better control of the retinopathy long-term.[6] The benefits of better glucose control systemically outweigh any local ocular risks.

Primary care physicians should be made aware that this drug might cause DR progression, and ideally all patients should get their routine DR screening prior to initiation of the drug. Once established with an ophthalmologist, increased screening for any diabetic retinopathy progression compared to normal re-examination timelines is recommended to catch any complications early. If the retina specialist is noting rapid progression on exam, earlier anti-VEGF may mitigate some of these changes. The PANORAMA trial showed us that anti-VEGF in patients with moderately severe to severe NPDR without diabetic macular edema can show a 2-step or greater improvement on the Diabetic Retinopathy Severity Scale, with significantly fewer vision-threatening complications.[7]

More guidance regarding this topic is being actively studied. The currently ongoing FOCUS trial is the first trial to evaluate the long-term effects of semaglutide on DR in patients with type 2 diabetes. This clinical trial will measure the presence of early treatment diabetic retinopathy level progression in 1500 patients with an A1c between 7% and 10%.8 Patients will be randomized to receive either placebo or semaglutide in addition to their diabetes medications, with the primary outcome of progression of DR and secondary outcomes of the incidence of treatment with anti-VEGF injections, laser photocoagulation, or vitrectomy. The study is estimated to conclude in 2026-2027.[8]

References:

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NJRetina continuously conducts clinical trials at key locations. Our clinical research coordinators will be happy to discuss the inclusion/ exclusion criteria or any other aspect of these studies with you or your patients. If you have any questions, please feel free to contact:

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Enrolling Studies:

Wet AMD
Edison
Opthea Coast: A Phase 3, Multicenter, Double-masked, Randomized Study to Evaluate the Efficacy and Safety of Intravitreal OPT-302 in Combination with Aflibercept, Compared with Aflibercept Alone, in Participants with Neovascular Age-related Macular Degeneration (nAMD)

Toms River
Opthea ShORe: A Phase 3, Multicenter, Double-masked, Randomized Study to Evaluate the Efficacy and Safety of Intravitreal OPT-302 in Combination with Ranibizumab, Compared with Ranibizumab Alone, in Participants with Neovascular Age-related Macular Degeneration (nAMD)

Teaneck
Luna: A Multi-Center, Randomized, Double-Masked Phase 2 Study to Assess Safety and Efficacy of ADVM-022 (AAV.7m8-aflibercept) in Anti-VEGF Treatment Experienced Patients with Neovascular (Wet) Age[1]related Macular Degeneration

Diabetic Retinopathy
Teaneck
Ocuterra: A Phase 2 Randomized, Double-Masked, Vehicle[1] Controlled, Multicenter Study to Evaluate the Safety and Efficacy of OTT166 Ophthalmic Solution in the Treatment of Diabetic Retinopathy (DR)

Upcoming Studies:

RVO
Teaneck, Toms River, Edison
Bayer Study: A Randomized, Double-Masked, Active-Controlled, Phase 3 Study of the Efficacy and Safety of Aflibercept 8 mg With Macula Edema due to Retinal Vein Occlusion

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