

GLP-1 RECEPTOR AGONISTS AND DR



Considerations for when your patient starts treatment with this type of medication for type 2 diabetes.

BY ISHANI KAPOOR, BS, AND MAJDA HADZIAHMETOVIC, MD

Diabetic retinopathy (DR), a microvascular complication of diabetes, is the leading cause of preventable blindness in the working-age population.¹ A recent study estimated that, as of 2021, 9.60 million people in the United States are living with DR, corresponding to a prevalence rate of 26% among those with diabetes. Moreover, 1.84 million people have visually threatening DR, about 5% of patients with diabetes.² Adequately controlling diabetes is imperative to prevent diabetic eye complications, and, fortunately, novel drugs to treat this disease are under investigation. One popular second-line diabetes treatment option is incretin-mimetic glucagon-like peptide-1 receptor agonists (GLP-1 RAs). These medications have been proven to lower hemoglobin A1c levels, promote weight loss, and provide cardiovascular benefits without the risk of hypoglycemia in patients with type 2 diabetes.³ The first GLP-1 RA was FDA-approved in 2005, and six are currently available on the market.^{3,4}

ABOUT GLP-1 RAS

GLP-1 is an endogenous hormone that stimulates insulin release in response to an oral glucose load.⁵ GLP-1 RAs increase the endogenous GLP-1 hormone activity, which can be blunted in patients with type 2 diabetes, thus improving diabetic control.⁵ The GLP-1 hormone has effects beyond the pancreas, including delayed gastric emptying, improved cardiac contractility and decreased risk of cardiovascular events, increased satiety, and reduced systemic inflammation.^{5,6}

Research is ongoing to understand the various tissues the GLP-1 hormone affects. Multiple experimental cell and animal studies have suggested that GLP-1 may directly reduce the progression of retinal disease through antiapoptotic and antiinflammatory mechanisms.⁶ Research on the diabetic retinas of *Caenorhabditis elegans* suggested that administration of a GLP-1 RA helped protect the organisms' retinal vasculature and neuroretinal function.⁷ While this discovery is promising, it warrants additional investigations to fully validate its potential implications in humans.

IN EYE CARE

GLP-1 RAs garnered attention in the field of ophthalmology when the SUSTAIN-6 Cardiovascular Outcome Trial (CVOT) reported a significantly increased risk of DR in the group treated with semaglutide versus placebo (hazard ratio = 1.76).⁸ The authors attributed this adverse outcome to the large and rapid fall in hemoglobin A1c levels during the initial 16 weeks of the trial^{9,10}; these patients had pre-existing DR and were receiving insulin. This trial, conducted in 2016 with a 104-week follow-up, occurred prior to widespread real-world use of this medication group and examined cardiovascular rather than ocular outcomes. Consequently, it may not have been adequate for evaluating the long-term stabilization or improvement of retinal pathology following a sudden, drastic decrease in hemoglobin A1c levels.

Clinical trials evaluating other GLP-1 RAs have also reported higher incidences of DR; however, none achieved statistical significance. The LEADER CVOT trial found a higher incidence of DR-associated events in a group treated with liraglutide compared with placebo.¹¹ The REWIND CVOT trial reported worse ocular outcomes (requiring photocoagulation, anti-VEGF therapy, or vitrectomy) in patients treated with dulaglutide compared with placebo.¹² These medications also produce a significant rapid fall in hemoglobin A1c, which may explain the increased incidence of DR and/or its progression.

DETERMINING THE CONNECTION

The results of these clinical trials prompted an important research question: Do GLP-1 RAs cause or worsen DR? Multiple published studies have tried to elucidate the answer. A 2021 meta-analysis of the CVOT studies of GLP-1 RAs identified no relationship between GLP-1 RA treatment and DR but did find that reduction in hemoglobin A1c was significantly associated with increased risk of DR over 1 year of follow-up.¹³ Our team conducted a meta-analysis of all GLP-1 RA randomized clinical trials (RCTs) and found that albiglutide, an FDA-approved medication that is no longer available in the United States, was associated with an increased risk of DR.^{14,15} We did not find that any other

GLP-1 RAs were associated with a significantly increased risk of worsening DR.¹⁴

Given the results of the SUSTAIN-6 trial,⁸ semaglutide has generated much discussion and uncertainty. A 2018 meta-analysis of RCTs found that semaglutide was not associated with the progression of DR compared with both placebo and other antidiabetic medicines.¹⁶ A 2021 meta-analysis of semaglutide RCTs found no association with increased DR risk when all trials were combined, although this result did not reach statistical significance.¹⁷ However, a subgroup analysis revealed that there was a significantly increased risk of worsening DR with semaglutide for patients 60 years of age or older and for those who had diabetes for 10 years or more.¹⁷

Notably, these clinical trials were not designed to study ocular outcomes, and DR was reported as an adverse event, not a primary outcome. Furthermore, the RCTs differed in DR-related criteria and methodology.

A recent observational study found that rates of DR progression with GLP-1 RA treatment were comparable with those of patients receiving no hypoglycemic agents.¹⁸ Another study using data from the Swedish Registers found a significantly lower risk of DR among patients who used a GLP-1 RA compared with those who did not.¹⁹

A 2023 meta-analysis of six observational studies reported no DR risk associated with GLP-1 RA use.²⁰ Furthermore, the results remained consistent across subgroup and sensitivity analyses, indicating no variation in DR incidence or progression; however, the authors stated that results were inconclusive due to wide confidence intervals.²⁰

WAITING ON BETTER CLARITY

Recently published literature on GLP-1 RAs and DR has failed to demonstrate a reliable and consistent adverse correlation between this medication group and retinal pathology. It is possible that the transient worsening of DR can be explained by the rapid drop in hemoglobin A1c levels. Other contributing factors that could perhaps influence this relationship include the level of pre-existing retinopathy, initial hemoglobin A1c levels, duration of diabetes, cotreatment with insulin, and comorbidities.

A dedicated 5-year ophthalmic clinical trial, FOCUS, is assessing the long-term effects of semaglutide on DR development and progression.²¹ The primary endpoint is the progression of DR, with 17 secondary retinal endpoints.²¹ Until the preliminary results are available, active follow-up with ophthalmology is warranted, including screening for DR before initiating treatment with a GLP-1 RA, as well as close follow-up during the initial treatment period.

A COLLABORATIVE APPROACH

Ophthalmologists should work closely with the patient's primary care team and be aware of changes to their

diabetic regimen; semaglutide, dulaglutide, and tirzepatide each come with patient safety warnings to speak with a doctor before starting treatment if they have DR. Therefore, it is important for ophthalmologists to stay up to date on the potential factors influencing the effect of GLP-1 RAs on the retina. Discussions of risk versus benefit may include considerations of patient characteristics, such as history of DR, poor glycemic control, markedly elevated hemoglobin A1c, duration of diabetes, and other medications, particularly insulin. ■

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