Does Saving the Kidneys Mean Risking the Eyes?

By Cindy X. Cai, Ian C. Han, and Jia Hwei Ng

Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) such as semaglutide have been a breakthrough therapy for many patients with type 2 diabetes and/or obesity. Beyond weight loss and improved glucose control, GLP-1 RAs can lower the rate of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke (1). Moreover, a recent study has shown that semaglutide reduced the risk of adverse kidney outcomes and death from cardiovascular causes in patients with chronic kidney disease, with outcome events being 24% lower in the semaglutide group than in the placebo group (2). Additionally, the mean annual estimated glomerular filtration rate decrease was slower by 1.16 mL/min/1.73 m^2 in the semaglutide group.

Recently, however, concern has arisen regarding the negative consequences of GLP-1 RAs for the eyes. For example, in SUSTAIN 6 (Trial to Evaluate Cardiovascular and Other Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes), those receiving semaglutide had significantly higher rates of retinopathy-related complications, including vitreous hemorrhage and diabetes-related blindness, and were more likely to require ocular treatment such as intravitreal injections or pan-retinal photocoagulation (1). A recent study linked semaglutide with a rare and potentially blinding eye condition known as nonarteritic anterior ischemic optic neuropathy (NAION) (3).

In the ophthalmic community, there is ongoing debate regarding the best response to these emerging data. The increased rates of diabetic retinopathy complications are not surprising. For example, the phenomenon of initial worsening of retinopathy with intense glucose control has been known since the 1980s from the landmark Diabetes Control and Complications Trial among patients with type 1 diabetes mellitus (4). Also, the paradoxical worsening with improved glucose control may not be overly concerning given the effectiveness of available treatments—appropriate and timely treatment of vision-threatening diabetic retinopathy reduces the risk of blindness by more than 90% (5). Furthermore, the finding of an increased rate of diabetic retinopathy complications has not been replicated in larger retrospective studies of semaglutide (6).

More worrisome, perhaps, is the recent article suggesting a potential association with semaglutide and NAION (3). NAION is a rare ischemic injury to the optic nerve affecting 2–10 per 100,000 people per year and resulting in blindness in nearly one-quarter of affected patients (7, 8). Unlike complications of diabetic retinopathy, there are no reliable treatments to restore vision loss from NAION (9). The potential association between semaglutide and NAION, however, requires more investigation. Notably, the recent study had many limitations, including its potential for inclusion bias (i.e., only patients referred to a subspecialty neuro-ophthalmology clinic at a tertiary care hospital were analyzed) and its use of relatively small numbers for comparison (17 patients with NAION on semaglutide versus 6 in the comparison group). The authors are also quick to note that demonstrating a potential association does not prove causality, especially in the absence of a clear mechanism. A larger, retrospective, multicenter population-based cohort study, for example, via the Observational Health Data Sciences and Informatics network (10), is needed to provide further clarity on this controversy.

Nephrologists should be aware of these potential eye issues with GLP-1 RAs. Until further data are available, nephrologists should continue prescribing GLP-1 RAs, but cautiously, and also should ensure that their patients are up to date with recommended ophthalmic screenings and have proper access to ophthalmic care. ■

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