GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS


Studies evaluated the effects of these drugs on IOP and glaucoma.

BY VIVIAN L. QIN, MD, AND VICTORIA L. TSENG, MD, PHD

ASSOCIATION BETWEEN GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS EXPOSURE AND INTRAOCULAR PRESSURE CHANGE: GLP-1 RECEPTOR AGONISTS AND INTRAOCULAR PRESSURE CHANGE

Hallaj S, Halfpenny W, Chuter BG, Weinreb RN, Baxter SL, Cui QN[1]

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ABSTRACT SUMMARY

This retrospective clinical cohort study evaluated the effect of glucagon-like peptide-1 receptor agonists (GLP-1RAs) on IOP in a population of patients in the University of California Health Data Warehouse. A change in IOP after exposure to GLP-1RAs was the primary outcome measure.

The study included 1,247 eyes of 626 patients undergoing therapy with GLP-1RAs and 1,083 eyes of 547 patients treated with other oral antidiabetic medication. All patients were at least 18 years of age, had at least one IOP measurement recorded within 1 year before and after the initiation of antidiabetic medication, and were naïve to glaucoma surgery or treatment.

The difference between pre- and postexposure IOP (change in IOP) and the difference between pre- and post-exposure IOP variance were analyzed using a paired t-test and generalized estimating equations. The mean changes in IOP were -0.4 ±2.8 mm Hg (paired t-test $P < .001$) and -0.2 ±3.3 mm Hg (paired t-test $P = .055$) in the GLP-1RA and oral medication groups, respectively.

IOP variability before and after exposure was also studied for 377 eyes of 167 patients for which there were at least three pre- and three post-tonometry records. There were no significant differences in IOP standard deviation before or after exposure in either group.

Although there was a significant decrease in IOP in the GLP-1RA group in the paired t-test analysis, GLP-1RA use was not independently associated with a change in IOP in the multivariable analysis.

DISCUSSION

What are the possible mechanisms by which GLP-1RAs may lower IOP?

GLP-1RAs have been associated with a reduced incidence of glaucoma in large-scale retrospective case-control studies[2,3] and with IOP lowering in a mouse model of hypertensive glaucoma.[4] A preclinical study of hydrocephalus showed that GLP-1RAs inhibited Na+/K+ ATPase activity within the choroidal plexus, decreasing cerebrospinal fluid production.[5] Given that Na+/K+ ATPase activity is also critical for aqueous humor production in the ciliary body, it is possible that

STUDY IN BRIEF

- A retrospective clinical cohort study used the University of California Health Data Warehouse to evaluate the effect of glucagon-like peptide-1 receptor agonists (GLP-1RAs) on IOP. The mean changes in IOP were -0.4 ±2.8 mm Hg (paired t-test $P < .001$) and 0.2 ±3.3 mm Hg (paired t-test $P = .055$) in the GLP-1RA and oral diabetic medication groups, respectively. Although the association was statistically significant, the use of GLP-1RA was not associated with a change in IOP in the multivariable analysis. None of the eyes had a history of glaucoma treatment.

WHY IT MATTERS

This was an initial real-world examination of the association between exposure to GLP-1RAs and IOP change. The IOP difference was small, and the use of GLP-1RA was not an independent predictor of IOP difference. The study nevertheless provides a strong foundation for further investigations into this relationship and adds to the existing literature on the potential benefit of GLP-1RA in glaucoma.

GLP-1RAs inhibit this ATPase activity and aqueous humor secretion, thereby reducing IOP.

Another explanation posited by Hallaj et al was that the weight loss effect of GLP-1RAs might be related to decreased IOP, based on a prior study of the role of excess weight in IOP.[6] The change in body mass index in the current study was not associated with the change in IOP, but the study was not sufficiently powered for a definitive conclusion.

What are the potential implications for real-world practice?

The clinical study by Hallaj and colleagues was an initial examination of the association between exposure to GLP-1RAs and the change in IOP that used real-world patient data.

Although the mean change in IOP in the GLP-1RA group was significant in the paired t-test analysis, the decrease of 0.4 mm Hg may not be a clinically relevant change.

Exposure to GLP-1RA was not independently associated with the change in IOP in the regression models. In the multivariable generalized estimating equation analysis, only preexposure IOP was found to be an independent predictor of IOP change. In the subgroup of patients with a preexposure IOP of at least 15 mm Hg, there was a mean IOP change of -1.44 mm Hg. Other subgroups associated with significant IOP change that were identified in the univariable analysis included patients with a diagnosis of glaucoma, patients with hypertension, and patients with hyperlipidemia. These subgroups may therefore represent useful avenues for further specific investigation.

The study had inherent limitations common to retrospective studies. Variables such as varying dosages of GLP-1RA and differences in patient characteristics between the groups were uncontrolled. The study nevertheless provides a strong basis for future investigations into the relationship between GLP-1RAs and IOP.

ASSOCIATION BETWEEN GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS AND THE RISK OF GLAUCOMA IN INDIVIDUALS WITH TYPE 2 DIABETES

Niazi S, Gnesin F, Thein AS, et al[3]

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ABSTRACT SUMMARY

This observational case-control study examined the association between GLP-1RA use and incident glaucoma in the Danish population. Danish national patient, prescription, death, and demographic registries were assessed. The study population included individuals with diabetes mellitus who were 21 years of age or older and were treated with metformin and a second-line antihyperglycemic agent after May 2007. GLP-1RA use was assessed through the prescription registry, and the outcome was incident glaucoma measured by International Classification of Diseases diagnosis code. Cases of incident glaucoma were density matched to the control group by sex and birth year in a 1:5 fashion. Conditional logistic regression was performed to evaluate the association between GLP-1RA use and glaucoma overall. A sensitivity analysis was performed that included individuals who initiated GLP-1RA treatment before 2007.

The study included 264,708 individuals, with 1,737 cases of incident glaucoma and 8,685 controls. In adjusted analyses, GLP-1RA ever-use was associated with decreased hazards of incident glaucoma (hazards ratio [HR] = 0.81, 95% CI = 0.70–0.94). There were no statistically significant associations, however, between GLP-1RA use for 0 to 1 and 1 to 3 years and incident glaucoma (HR = 0.89, 95% CI = 0.70–1.14 and HR = 0.85, 95% CI = 0.67–1.06 for 0–1 and 1–3 years, respectively). In contrast, GLP-1RA use for greater than 3 years was associated with a decreased risk of glaucoma (HR = 0.71, 95% CI = 0.55–0.91). The sensitivity analysis produced similar results.

DISCUSSION

What are the mechanisms by which GLP-1RAs may exhibit neuroprotection in glaucoma?

GLP-1RAs are commonly prescribed for the treatment of diabetes mellitus and obesity. Activation of the GLP-1R pathway in the central nervous system triggers a cascade that inhibits the release of proinflammatory cytokines and promotes cell survival.[7,8] In some animal models of Parkinson disease and Alzheimer disease, GLP-1RAs have mitigated the degree of neuron loss and reduced behavioral symptoms of disease.[9] NLY01 is a GLP-1RA with favorable blood–brain barrier penetration. It was used in a mouse model of glaucoma to test the effect of GLP-1RA on retinal inflammation and retinal ganglion cell death. After ocular hypertension with a release of proinflammatory cytokines was induced, treatment with NLY01 led to a reduction in astrocyte transformation and retinal ganglion cell death.[10] These findings support the notion that GLP-1RAs may demonstrate neuroprotective mechanisms in glaucoma by modulating neuroinflammatory processes.

What are the implications of this study for real-world practice?

Currently approved therapies for glaucoma are limited to medications and surgeries that reduce IOP to slow disease progression. Neuroprotective therapies for glaucoma have long been sought by both glaucoma specialists and patients. The consistency in epidemiologic findings from the present study combined with laboratory findings in animal models suggest that GLP-1RAs may hold potential as a neuroprotective option for glaucoma treatment.

STUDY IN BRIEF

▶ A large case-control study drew on multiple Danish registries to examine the association between glucagon-like peptide-1 receptor agonist (GLP-1RA) use and incident glaucoma. Both GLP-1RA ever-use and greater than 3 years of use were found to be associated with decreased hazards of incident glaucoma.

WHY IT MATTERS

The consistency in epidemiologic findings from this study and laboratory findings in animal models indicate that GLP-1RAs hold potential as a neuroprotective option for glaucoma treatment. A randomized clinical trial is required to address the limitations of observational studies and provide further information on the potential of GLP-1RAs for glaucoma therapy.

Randomized clinical trials in representative populations are required to investigate the possibility of routine GLP-1RA use to treat glaucomatous neuropathy. Existing observational studies have several potential sources of bias. For example, the diagnosis of glaucoma and use of GLP-1RAs are subject to misclassification in administrative databases. Furthermore, the assessment of the clinical features and severity of glaucoma is limited by International Classification of Diseases diagnosis codes. Any observational study, moreover, can be confounded by unmeasured demographic, systemic, and lifestyle factors. The implementation of a randomized trial would address these factors and provide further information on GLP-1RAs' potential as an innovative neuroprotective treatment for glaucoma. ■

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JAMES C. TSAI, MD, MBA | SECTION EDITOR
- President, New York Eye and Ear Infirmary of Mount Sinai, and Delafield-Rodgers Professor and System Chair, Department of Ophthalmology, Icahn School of Medicine at Mount Sinai, New York
- Member, *GT* Editorial Advisory Board
- jtsai@nyee.edu
- Financial disclosure: Consultant/advisory board (AI Nexus Healthcare, Eyenovia, Smartlens)

VIVIAN L. QIN, MD
- Assistant Professor, Doheny Eye Institute, Stein Eye Institute, University of California, Los Angeles
- vqin@mednet.ucla.edu
- Financial disclosure: None

VICTORIA L. TSENG, MD, PHD
- Assistant Professor, Department of Ophthalmology, and Director for the UCLA Ophthalmology Residency, University of California, Los Angeles
- vtseng@mednet.ucla.edu
- Financial disclosure: None