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ORIGINAL RESEARCH

Incidence of Glaucoma or Ocular Hypertension After Repeated Anti-Vascular Endothelial Growth Factor Injections for Macular Degeneration

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Purpose: To estimate the risk of glaucoma or sustained ocular hypertension (OHT) related to anti-vascular endothelial growth factor (VEGF) injections for age-related macular degeneration (AMD).

Design: Retrospective chart review.

Subjects: Patients who received unilateral anti-VEGF injections for AMD at the Wheaton Eye Clinic (IL).

Methods: Chart analysis was performed on 1095 patients, without prior glaucoma or OHT, who received unilateral anti-VEGF injections for AMD from 2005 to 2012, with data collected through 2013. Data collection included demographics, lens status, date and medication type of each injection, and the date of diagnosis of glaucoma or OHT by a treating glaucoma specialist, which was the main outcome measure. Rare events logistic regression was performed to determine the risk of disease development based on sex, lens status, and injection frequency.

Results: Unilateral glaucoma or sustained OHT developed in 42 patients over the course of follow-up, with 40 events in the injected eye only, 2 in the contralateral eye only. Statistical modeling predicted elevated risk for onset of glaucomatous disease with a higher maximum frequency of injections ($p < 0.0001$, odds ratio [OR] 2.18 for each additional injection over the most injection-intense 6 months for a given subject) and with phakic lens status ($p = 0.0009$, OR 0.33 for pseudophakia).

Conclusion: Our results show a significant risk for glaucoma or OHT development in patients undergoing repeated treatments with intravitreal anti-VEGF injections for AMD, establishing the first reliable connection between disease development and a period of high-frequency injections. In addition, we show a significantly increased risk of disease development in phakic patients, which we believe points to a mechanical explanation for this type of secondary glaucoma.

Keywords: exudative macular degeneration, secondary glaucoma, open-angle glaucoma, anti-vascular endothelial growth factor

Introduction

Anti-vascular endothelial growth factor (VEGF) injections have become the mainstay of treatment for exudative age-related macular degeneration (AMD), with annual increases in the total number of injections from 2006 to 2015 in the United States.[1] Currently available agents have been extensively studied for their benefit in AMD treatment and include ranibizumab (Lucentis; Genentech, South San Francisco, CA)[2–4] and aflibercept (Eylea; Regeneron, Tarrytown, NY),[5] both of

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which have been approved by the US Food and Drug Administration (FDA) for the treatment of neovascular AMD, and the non-FDA approved bevacizumab (Avastin; Genentech).[6,7]

Adverse events from anti-VEGF treatment have been extensively reported in many 1- to 2-year clinical trials,[2–7] and the incidence of ocular and systemic adverse events has been low. For example, a recent meta-analysis of 10 aflibercept trials for the treatment of various retinal diseases reported no difference between treated patients and controls for intraocular inflammation, endophthalmitis, or selected systemic adverse events.[8]

Nonetheless, various authors have reported glaucoma or sustained ocular hypertension (OHT) development associated, at least temporally, with intravitreal anti-VEGF injections.[9–15] It is not surprising, of course, that an immediate rise in intraocular pressure (IOP) would be seen after an intravitreal injection, as a volume of fluid is added to the restricted intraocular space. A study of 213 consecutive injections in AMD patients showed that the mean immediate post-injection IOP was 44 mmHg but fell to <30 mmHg in 96% of patients by 15 mins and in 100% of patients within 30 mins.[16]

A strong, or even causative, link between repeated intravitreal anti-VEGF injections and glaucoma development has been difficult to assess over a large population of injected patients. However, there are reasons to believe that repeated intravitreal injections with anti-VEGF agents may decrease the function of the aqueous outflow system and be associated with the development of glaucomatous disease. Wen et al recently showed that aqueous outflow facility was reduced by 12% in eyes undergoing 20 or more anti-VEGF injections for AMD, compared to uninjected fellow eyes.[17] The same study showed no decrease in outflow facility for eyes receiving 10 or fewer injections. Separately, subjects receiving monthly ranibizumab injections for 2 years, as part of the MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab) and ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD) trials,[2–4] were evaluated for the incidence of elevated IOP across study visits, when IOP was measured prior to that day's injection.[18] The authors showed that the incidence of IOP >25 was significantly higher in the injection group (10.9%) versus sham or photodynamic therapy (PDT, 5.1% combined), and the incidence of an 8 mmHg IOP rise from baseline was 24.2% in the injection group, versus 13.6% in the sham or PDT subjects. In a separate analysis by Freund and colleagues of patients receiving every 4 weeks injections of ranibizumab (2 mg) or aflibercept (2 mg) as part of the VIEW (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD) 1 and 2 studies,[5] 19.7% of ranibizumab eyes and 14.1% of aflibercept eyes developed a 5 mmHg or greater IOP rise from baseline at some point over the 96-week study, confirmed on two consecutive visits.[19] However, the analogous proportions in untreated, fellow eyes, were 15.6% and 13.3%, respectively, clouding the interpretation. Also, regarding the potential difference in IOP outcomes between the two drugs, it is noteworthy that the ranibizumab group had a higher percentage of preexisting glaucoma, a higher baseline IOP, and a higher percentage of preexisting glaucoma medication use than the aflibercept group.

Database studies have also been performed, seeking to quantify the potential interaction between either anti-VEGF injections and glaucoma or between anti-VEGF injections and IOP. Recently published work based on a health database in British Columbia suggested that the risk of glaucoma surgery was greatly increased in patients receiving seven or more bevacizumab injections per year.[20] However, in this case–control study, over three-fourths of the included patients had pre-existing glaucoma, with implications regarding the effect of injections on glaucoma patients but perhaps not on the initial development of glaucoma itself. Atchison and colleagues used the American Academy of Ophthalmology Intelligent Research in Sight (IRIS) Registry to assess the proportion of patients undergoing injections at various thresholds who then displayed a sustained IOP rise of at least 6 mmHg from baseline to a value >21 mmHg.[21] A relatively low rate of sustained IOP rise is reported (2.6% compared to 1.5% in the untreated fellow eye), but there are limitations to this dataset, including the absence of data on glaucoma medication use.

The presented research attempts to answer the fundamental question of whether the development of glaucoma or sustained OHT can be reliably linked to repeated intravitreal anti-VEGF injections in AMD patients. We report, to our knowledge, the largest chart review yet submitted to answer this question, while limiting our dataset to patients in whom unilateral injections were performed but both eyes were amenable to analysis for possible glaucoma development. Importantly, full chart reviews were performed on all patients, enabling us to be certain of the timing and extent of any IOP rise, and allowing us to judge

outcomes based on a confirmed diagnosis of glaucoma or OHT by a treating glaucoma specialist. In addition, thorough statistical modeling was performed to analyze the risk of these diagnoses under varying injection and demographic parameters.

Methods

Chart analysis was performed in patients receiving at least one intravitreal injection at the Wheaton Eye Clinic (Wheaton, IL) from January 1, 2005, to December 31, 2012. Follow-up data were collected through December 31, 2013. The described research adheres to the tenets of the Declaration of Helsinki as well as all relevant federal and state laws. The study protocol was reviewed and approved by the Ethics Committee of the Wheaton Eye Clinic. The requirement for informed consent was waived due to the anonymized and retrospective nature of the study.

Charts were obtained for analysis by an internal billing query of the Current Procedural Terminology code for intravitreal injection, matched with any International Classification of Diseases-9 AMD code. A total of 3081 potential subjects were identified in this way. Individual charts were then accessed to complete further screening, selecting only patients who had the correct, exudative AMD diagnosis, and limiting the dataset to exclude any patient with a history of bilateral injections, a prior diagnosis of glaucoma or OHT before the first injection, or diseases of the contralateral eye that could lead to non-diagnosis or non-treatment of glaucoma. Examples of this last exclusion condition included fellow eye non-glaucomatous optic neuropathies, light perception or no light perception vision prior to the first injection, or true monocular status. Twelve incomplete cases due to missing demographic or injection data were also removed.

A total of 1095 subjects met inclusion criteria, and data were collected from the clinical charts, including sex, date of birth, lens status in both the study and fellow eye (categorized as already pseudophakic prior to first injection, still phakic after last injection, or date of cataract surgery), the date of each intravitreal injection categorized by medication used, and the date of last follow-up. Race or ethnicity documentation was not consistently present within the medical records and therefore could not be included within the demographic data. Seventeen subjects with the last follow-up date less than 30 days after the first injection were excluded. The remaining 1078 subjects were then assessed for the diagnosis of glaucoma or OHT in either the study or fellow eye by thorough, full review of each patient's clinical file, and the date of the elevated IOP leading to the diagnosis was called the event date. If an event was detected, the bilateral IOP on the date of detection was recorded, or, if treatment was not started on that date, and if bilateral Goldmann applanation tonometry (GAT) was not used, then the follow-up IOP by GAT, recorded at the glaucoma service consultation, was recorded.

All subjects with positive events in this study were referred from a retina specialist to a glaucoma specialist within the practice, and a complete glaucoma work-up was performed, typically including corneal pachymetry, optical coherence tomography of the retinal nerve fiber layer, and either automated or manual kinetic visual field testing, as required by each clinical situation. In no case was the onset of disease found to be diagnosed within a 90-day post-operative period (for example, after cataract surgery). All positive case diagnoses were associated with open angles by gonioscopic appearance in the opinion of the treating specialist, and in all cases chronic treatment regimens were introduced. In total, 63 positive events were identified, including 40 events in the injected eye only (22 initially diagnosed with OAG and 18 with sustained OHT requiring treatment), 2 events in the contralateral eye only (1 OAG and 1 OHT), and 21 events of bilateral disease (10 cases of OAG including 3 diagnosed as normal tension glaucoma and 11 OHT). Subjects who developed a positive event in only the contralateral eye or in both eyes were excluded from further risk modeling. It is noted that the opinion of the treating glaucoma specialist as to disease status and laterality has been used as the sole arbiter of event occurrence. This outcome measure was deliberately chosen to allow assessment of clinically significant disease occurrence requiring treatment and further monitoring, as opposed to an IOP-only strategy, with results that might be misinterpreted out of context, for example due to inaccurate or non-reproducible IOP readings, post-operative IOP spikes, or other clinically insignificant measurements that may cross a preset threshold. Descriptively, however, the 40 subjects diagnosed with unilateral glaucoma in the injected eye presented with a mean pre-treatment IOP of 34.9 mmHg (SD 9.7) in the treated eye versus 16.7 mm Hg (SD 2.9) in the contralateral eye. Thirty-eight of these 40 measurements were by GAT, as two Tonopen (Reichert, Depew, NY) measurements of 45 mmHg by retina specialists led to urgent treatment before the transfer of care to the glaucoma clinic.

There remained 1055 subjects for statistical modeling of disease risk, and the de-identified database of demographic information, lens status, list of injection dates, event dates, and last follow-up were then subjected to thorough statistical review. Injection information was used to compute the total number of injections (TOTINJ) during treatment and the highest number of injections given in any 6-month period (HIGH6MO). This HIGH6MO variable was included as a gauge of frequency of injections, to consider whether a series of closely spaced injections may be associated with some form of insult, or some lack of return to homeostasis, that may be associated with disease development. For patients with positive disease status, any injections received after the event date for glaucoma or OHT development were not included in the analysis. The majority of subjects received bevacizumab as the only administered medication, and there was not enough variation in medication data to model the potential effects of different medications. The proportion of bevacizumab injections was 78.8% and 78.2% of all injections in men and women, respectively, compared to 9.3% and 8.8% of injections with ranibizumab, and 10.8% and 11.4% of injections with aflibercept. Lens status was coded as "pseudophakic" if a patient underwent cataract surgery without a diagnosis of glaucoma or OHT, or underwent surgery prior to such a diagnosis, and "phakic" otherwise.

Disease status was modeled with a rare-events logistic regression method that corrects for bias in the estimates due to the scarcity of disease in the population.[22,23] Model selection was performed by both visual inspection of the relationships between disease status and potential explanatory variables and by penalized likelihood ratio tests. The model predicts the probability of disease by sex, age, TOTINJ, HIGH6MO, and pseudophakia.

Results

Demographic characteristics of the studied subjects are given in Table 1. Injection patterns by group are listed in Table 2, corresponding to the study variables listed above. The initial review of 1078 subjects identified 63 positive events, including 21 cases of glaucoma or sustained OHT diagnosed bilaterally. These bilateral events are presumed to relate to the underlying population risk for disease, and the incidence was 1.95% over the course of follow-up, with an average follow-up length of 32.01 ± 23.3 months. This is not dissimilar from incidence rates reported across broad populations, such as the Los Angeles Latino Eye Study (4-year incidence for open-angle glaucoma of 2.31% in a Latino population >40 years old)[24] or the Rotterdam Study (5-year incidence of definite or

Table 1 Demographic Characteristics of Patients by Injected Medication

	Bevacizumab Only	Pegaptanib Only	Ranibizumab Only	Aflibercept Only	Mixed Medications
Patients, no	812	11	18	28	186
Female, no (%)	511 (63%)	4 (36%)	11 (61%)	18 (64%)	117 (63%)
Age at first injection (years), mean (SD)	80.9 (8.5)	83.5(6.7)	81.8(7.8)	80.3(8.3)	77.0(7.77)
Total injections, mean no (SD)	6.9 (6.3)	3 (1.9)	6.7 (8.6)	8.3 (5.0)	16.3 (9.2)
Pseudophakia, %	57%	73%	72%	64%	53%
Average, Median follow-up (months)	31.1, 25.1	33.6, 28.7	28.2, 26.4	13.7, 14.7	39.2, 33.4
Range of follow-up (months)	1.1–92.3	5.9–93.3	1.1–69.9	1.8–22.2	5.9–94.7

Table 2 Injection Patterns by Lens and Event Status

	Non-Event Patients (No Diagnosis of Glaucoma or Sustained Ocular Hypertension), n=1015		Event Patients (Diagnosed with Glaucoma or Ocular Hypertension in Follow-Up), n=40	
	Total Injections (TOTINJ), Mean (SE)	Highest No. Injections in 6 Months (HIGH6MO), Mean (SE)	Total Injections (TOTINJ), Mean (SE)	Highest No. Injections in 6 Months (HIGH6MO), Mean (SE)
Male, Phakic	7.8 (7.1)	3.4 (1.2)	14.6 (11.4)	4.7 (1.2)
Female, Phakic	8.4 (7.6)	3.4 (1.2)	16.2 (5.8)	4.6 (1.3)
Male, Pseudophakic	8.6 (7.8)	3.5 (1.3)	22.0 (18.0)	4.8 (1.5)
Female, Pseudophakic	8.3 (7.8)	3.4 (1.2)	11.5 (6.9)	4.4 (1.6)

probable open-angle glaucoma 1.8% for age 65–69 years, 2.4% for 70–74 years, 2.6% for 75+ years).[25]

An additional 40 subjects developed glaucoma or sustained OHT in only the injected eye, while 2 subjects developed glaucoma or sustained OHT in only the untreated, contralateral eye. Therefore, 95.2% of patients diagnosed with unilateral disease developed the disease in the treated eye only. The time to disease development for these 40 subjects is displayed in Figure 1.

The final (or "reduced") logistic regression model predicts the probability of disease by sex, HIGH6MO, and pseudophakia. The initial, "full" model also included TOTINJ and age at first injection. These, however, were non-significant ($p = 0.68$ for TOTINJ and $p = 0.52$ for age) in the full model and therefore were eliminated from the final, "reduced" logistic regression. The results are reported in Table 3. It is noteworthy that TOTINJ is indeed highly significant if HIGH6MO is excluded from the full model ($p < 0.0001$ for TOTINJ under this scenario). These two variables are, in fact, correlated, as patients who received more frequent injections also tended toward a higher total number of injections (correlation = 0.65). HIGH6MO, however, is the better explanatory variable, as it remains highly significant ($p < 0.0001$), and TOTINJ becomes non-significant ($p = 0.68$), when both variables are included in the model.

Figure 2 shows the effect of the three explanatory variables on the probability of disease. There is some evidence of a difference in disease risk between men and women, with men displaying a higher risk. A higher rate of injections (the maximum rate over any 6-month period, up to approximately 1 injection per month) is associated with a significantly higher risk of disease development. Finally, there is evidence that pseudophakic patients were at a greatly reduced risk for disease development compared with phakic patients.

Table 4 gives the model results in terms of odds ratios. The odds of disease for females is 48% of the odds for males, albeit with a wide 95% confidence interval that stretches from 25% up to 92%. Similarly, the odds of disease for pseudophakic patients is only 33% of the odds of disease for phakic patients. For maximum injection rate, the odds ratio describes the change in the predicted probability of disease based on a one-unit change in the explanatory variable. For example, patients who receive a maximum of two injections over any 6-month period are predicted to be 2.18 times more likely to be diagnosed with glaucoma or sustained OHT than those whose maximum frequency is one injection over any

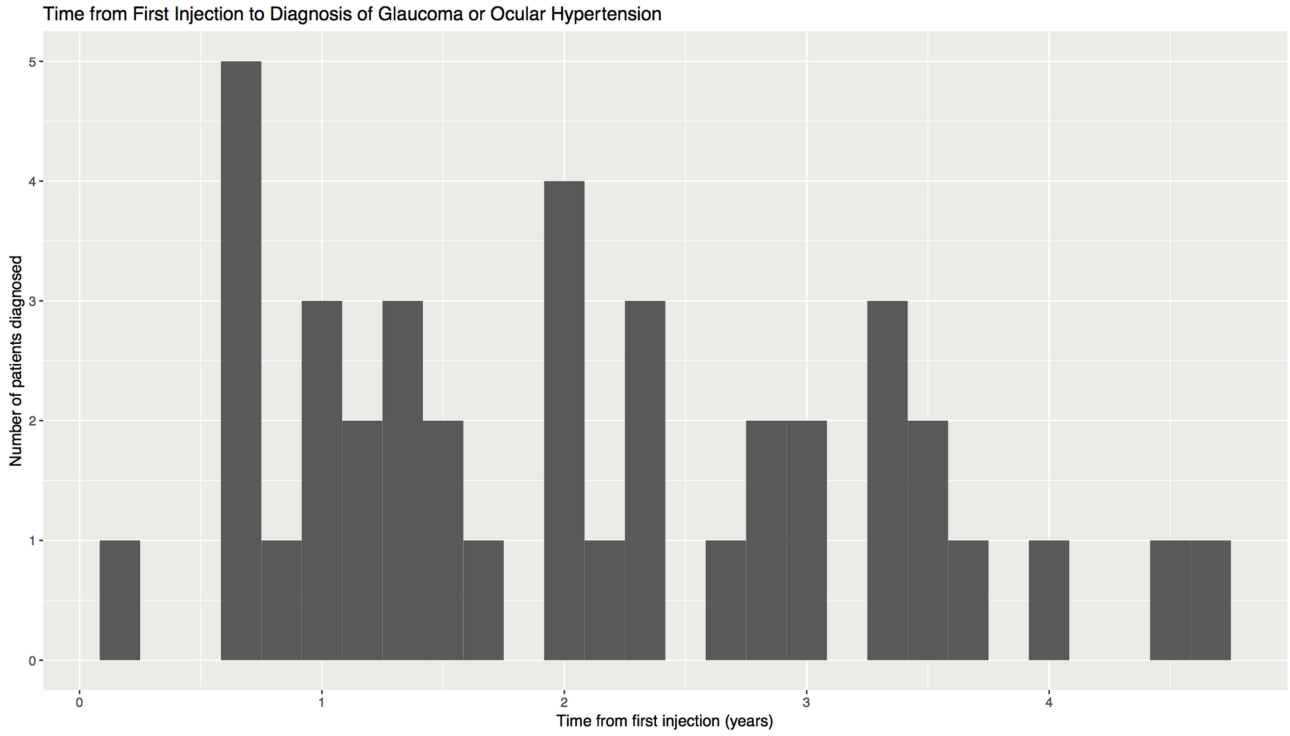

Figure 1 Histogram showing time from first intravitreal anti-vascular endothelial growth factor injection to development of glaucoma or sustained ocular hypertension, with each column representing 2 months. Incidence is distributed over 4+ years of follow-up, with 8 subjects developing disease before 1 year, 22 from years 1–3, and an additional 10 after 3 years from the first injection.

Table 3 Logistic Regression Results Predicting the Probability of Glaucoma or Sustained Ocular Hypertension

Variable	Coefficient	Standard Error	95% Confidence Interval	*p*-value
A. Reduced Model				
Sex (Female)	−0.73	0.33	(−1.40, −0.08)	0.028
HIGH6MO	0.78	0.14	(0.51, 1.07)	<0.0001
Pseudophakia	−1.12	0.35	(−1.85, −0.50)	0.0009
B. Full Model				
Sex (Female)	−0.75	0.33	(−1.41, −0.10)	0.024
HIGH6MO	0.75	0.18	(0.40, 1.11)	<0.0001
Pseudophakia	−1.20	0.37	(−1.97, −0.48)	0.0009
TOTINJ	0.01	0.02	(−0.03, 0.04)	0.68
Age at First Injection	0.01	0.02	(−0.02, 0.06)	0.52

6-month period. Applying this ratio to a three-unit difference, the model predicts a 10.40 times higher likelihood of disease when a patient's maximum frequency is, for instance, 6 injections versus 3 over any 6-month period.

Discussion

The modeled data show a distinctly increased risk for glaucoma or sustained OHT development in patients undergoing intensive treatment regimens with anti-VEGF

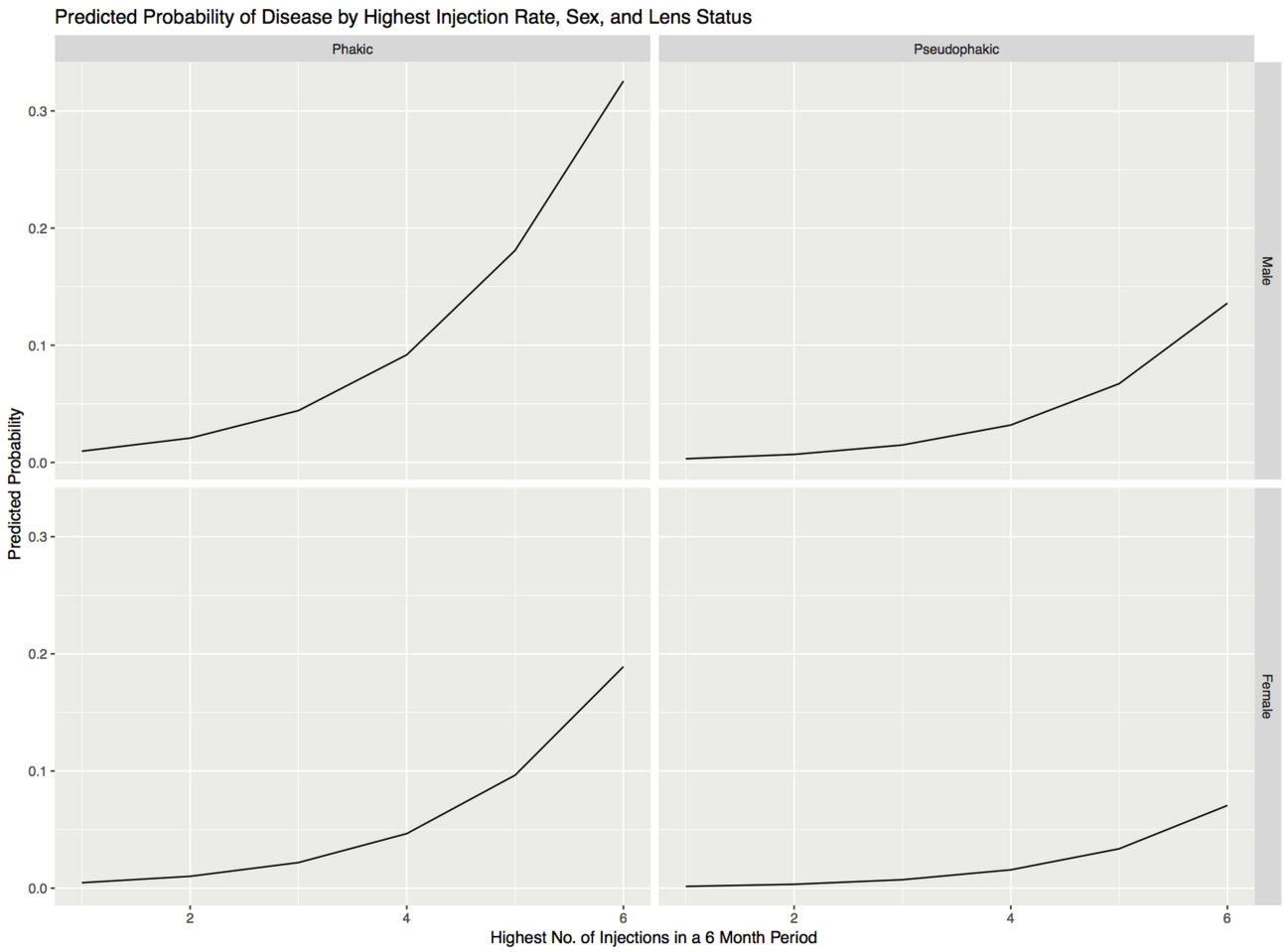

Figure 2 Using the results of the logistic regression (coefficients from the reduced model in Table 3), the predicted probability of disease is graphed against the highest injection rate over any 6-month period. This relationship is displayed distinctly for the four combinations of sex and lens status.

Table 4 Odds Ratios for Firth's Logistic Regression (See Table 3)

Variable	Odds Ratio	95% CI
Sex (Female)	0.48	(0.25, 0.92)
HIGH6MO	2.18	(1.66, 2.91)
Pseudophakia	0.33	(0.16, 0.64)

intravitreal injections for exudative AMD. Although odds ratios are reported and show an increased risk of glaucoma or OHT development with male sex, higher injection frequency, and phakic status, the data are best interpreted by modeling the effects of changes in the various parameters on probability of disease development.

The probabilities depicted in Figure 2 distinctly show that a 6-month period of high-frequency injections increases the predicted risk of disease significantly under all combinations of sex and lens status. For example, a phakic man with a 6-month high of five injections has a predicted 18.1% risk of disease, whereas a phakic man with a 6-month high of three injections has only a 4.4% estimated risk. This relationship may have implications for initiation and maintenance protocols in exudative AMD patients, favoring both lower frequency initiation therapy and extension of inter-injection intervals as possible with ongoing therapy (so-called treat-and-extend protocols[26]), presuming that similar clinical effectiveness in AMD treatment can be achieved. It is tempting to extend these data to favor one medication over another, if the same clinical effectiveness in AMD treatment can be achieved via less frequent injections of one medication versus another. However, our data cannot directly address this question given the preponderance of bevacizumab injections in our study set. In addition, the supposed advantage of a lower frequency but higher potency anti-VEGF injection regimen would only be beneficial as to glaucoma development if the effect is truly related to the injection event, as opposed to the pharmacologic VEGF blockage itself. This is a mechanistic question that cannot be fully answered but will be addressed below.

The data give convincing evidence of a relationship between lens status and disease development, and this may be instructive regarding the mechanism that leads to glaucoma or sustained OHT. We undertook this study to assess for a positive link, or lack thereof, between anti-VEGF injections and glaucoma or sustained OHT development. The fact that 95.2% (40/42) of patients diagnosed with unilateral glaucoma or sustained OHT during follow-up developed the disease in the injected eye, as opposed to the uninjected fellow eye, seems to establish this link quite securely. The fact that pseudophakia proved greatly protective may begin to suggest the disease mechanism, and in our analysis, this finding, more than any other, supports a mechanical cause for the disease. Potential medication-induced explanations for cases of post-injection glaucoma or sustained OHT have included clogging of the trabecular meshwork with silicone oil droplets[27] or aggregated proteins,[28] altered nitric oxide metabolism,[29] or a direct effect of VEGF blockage on trabecular endothelial permeability,[30] as reviewed by Aref.[31] However, it is unclear why these effects, which presumably would operate at the level of the trabecular meshwork, would be greater in phakic eyes than in pseudophakic eyes, as clinical observation suggests that substances injected into the vitreous cavity are more likely to migrate to the anterior chamber, or are likely to migrate faster, in a pseudophakic eye than in a phakic one. This effect was seen in one study of intravitreal triamcinolone acetonide (TA) injections, where TA crystals were observed in the anterior chamber 1 hr after injection in 5 of 31 pseudophakic patients, but no anterior chamber crystals were observed at this time point in the 57 phakic patients who received injections.[32]

In our opinion, the predominance of glaucoma and sustained OHT in phakic patients following a series of intravitreal anti-VEGF injections align well with a mechanical theory of outflow system damage. This damage is presumably related to the process of the injections themselves, where the repeated injections of volume into the restricted space of the vitreous cavity create an immediate and substantial pressure imbalance between the vitreous cavity and the areas anterior to the lens that are filled with aqueous humor. As the zonular system suspending the lens is not indefinitely rigid, it is hypothesized that the anterior chamber volume compresses, as shown by Kerimoglu et al after TA injections,[32] with anterior movement of the lens and iris. This movement may strain the outflow apparatus, perhaps at the longitudinal fibers of the ciliary muscle, thereby compromising outflow facility over time with repeated injections. Our data regarding injection frequency suggest that a sufficient return to homeostasis between injections may diminish the long-term risk of outflow system damage.

The strain on the outflow system may be reduced both by a more rapid volume equilibration from posterior to anterior through the zonules of the pseudophakic patient and by the quicker resolution of the immediate post-injection IOP spike that seems to occur in pseudophakic

patients,[32] perhaps due to the more widely open anterior chamber angle compared to phakic eyes. Alaghband and colleagues recently showed, using electronic Schiotz tonography, that outflow facility was improved 3, 6, and 12 months post-operatively following modern phacoemulsification cataract surgery.[33] Improved outflow facility in pseudophakic patients would naturally lead to quicker resolution of post-injection IOP spikes.

A decrease in outflow facility was in fact seen by Wen and colleagues after 20 intravitreal anti-VEGF injections, compared to the uninjected fellow eye.[17] Further, Wen and colleagues evaluated 21 patients following intravitreal anti-VEGF injection, showing that there was significantly more narrowing of the nasal angle in phakic compared to pseudophakic eyes.[34] This suggests that, following an injection, volume equilibration from posterior to anterior was more rapidly achieved in the pseudophakic group, again supporting our hypothesis, as described above. One author (JBW) notes that, clinically, patients undergoing cataract surgery after a history of repeated intravitreal injections are more likely to demonstrate shallowing of the lens capsule after lens nucleus removal, suggesting a generalized deficiency in zonular turgidity that may be consistent with the mechanism described. A subtly alternative hypothesis would be to suggest that pseudophakia is not so much protective against the anti-VEGF injection-induced damage to the outflow apparatus, but instead the pseudophakic eye, with its outflow facility already improved from baseline because of the prior cataract surgery, can still maintain a normal IOP even if outflow facility is later degraded by a series of injections.

Our results are in step with early reports proposing a link between anti-VEGF injections and glaucoma development.[9–15] Our study extends current knowledge of this link and verifies it with far more statistical power. Our results are also consistent with the recent analyses applied to MARINA and ANCHOR, as well as VIEW 1 and 2 databases, showing that a proportion of patients developed significant IOP elevations after a series of ranibizumab or aflibercept injections.[18,19] Our study extends these findings by looking not just at IOP results but at the actual development of glaucomatous disease requiring treatment. Although it is outside the scope of this paper to describe patient experiences in terms of glaucoma severity and required treatment regimens, one author (JBW) has found it necessary to provide surgical glaucoma care, including filtering surgery, to numerous patients diagnosed with unilateral glaucoma following a series of same eye intravitreal anti-VEGF injections, underlining the significance of the problem in these patients.

With a link established between repeated intravitreal anti-VEGF injections and the development of glaucoma in certain patients, a number of questions follow, including those related to monitoring, treatment, and epidemiology. Our research cannot yet answer questions regarding disease severity in this population, but we can comment on the probability of disease with various patient factors and injection patterns. We show a high rate of disease in certain populations, especially phakic patients who have undergone a period of high-frequency injections. This level of detail in our analysis may explain why our risk prediction model does not appear to align particularly well with a recently published study of IOP results in patients undergoing anti-VEGF treatments from the IRIS Registry.[21] However, by its nature, a registry study is unable to individually assess charts for context, making these results very difficult to interpret for the question at hand. For example, the authors of this study were unable to assess or report the frequency of use of glaucoma medications, which would presumably have lowered the IOP in treated patients but would not necessarily have registered as a clinically significant IOP increase based on the analysis criteria. In addition, over concerns of data quality, subjects were eliminated from this IRIS Registry study if there were too many reported IOP values, or if there were reported IOPs between 0 and 5 mmHg. However, a subject diagnosed with glaucoma during the study period might naturally have undergone an increased number of IOP checks and potentially, after glaucoma surgery, have experienced a period of hypotony. In fact, over 70% of initially screened registrants were eliminated from the analysis in this study due to lack of at least 1 baseline IOP value, lack of at least 1 IOP value after 1 year, or undergoing >75 IOP measurements. Then, 5.86% of the remaining subjects were eliminated from the analysis due to at least 1 IOP value between 0 and 5 mmHg. Finally, as our Figure 1 shows, it was not uncommon to find glaucoma or sustained OHT development even 3 years after the first anti-VEGF treatment, meaning that long-term follow-up and data analysis would be necessary to discover these cases.

In conclusion, our large chart review study shows a significant risk for glaucoma or sustained OHT development in patients undergoing repeated treatments with anti-VEGF intravitreal injections for exudative AMD. Further, we establish, to our knowledge, the first reliable

connection between disease development and a period of high-frequency injections. In addition, we show, also for the first time, a significantly increased risk of disease development in phakic patients, and we present a plausible explanation for these findings. The connection between glaucoma or sustained OHT development and both high-frequency injections and phakic status suggests, in our opinion, a mechanical basis for this complication of repeated intravitreal anti-VEGF treatments. Further study should evaluate these connections further, explore alterations in anti-VEGF treatment protocols that may confer a lower risk of this complication, and describe results of treatment for this recently described type of secondary glaucoma.

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Disclosure

The authors report no conflicts of interest in this work.

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