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Systemic Beta-Blockers in Neovascular Age-Related Macular Degeneration

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Abstract

Purpose—To evaluate whether oral beta-blockers (BB) are associated with a decreased number of intravitreal injections in patients with incident neovascular age-related macular degeneration (nAMD).

Methods—A retrospective cohort study of subjects with a new diagnosis of nAMD was conducted using a medical claims database from a large national US insurer. Two cohorts were created for comparison consisting of patients with regular use of BBs or calcium channel blockers (CCB). The main outcome measured was the difference in the mean number of intravitreal injections administered between the two cohorts.

Results—After inclusion and exclusion criteria, 239 BB and 155 CCB subjects remained for analysis. Univariate analysis revealed that the mean number of injections in the BB cohort was 6.43 (95% CI 5.90-6.95) versus 6.55 (95% CI 5.85-7.25) in the CCB cohort ($p=0.78$). After multivariate adjustment, the mean number of injections in the BB group was 6.32 (95% CI 5.77-6.87) versus 6.71 (95% CI 6.02-7.40) in the CCB group. The overall difference between the two groups was -0.39 (95% CI difference -1.29-0.51; $p=0.40$).

Conclusion—The use of oral beta-blockers is not associated with a decreased number of intravitreal injections in incident nAMD patients.

Keywords

Age-related macular degeneration; beta-blocker; choroidal neovascularization

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Introduction

Age-related macular degeneration (AMD) is the leading cause of blindness in older individuals in developed countries¹. Advanced stages of AMD, including choroidal neovascularization (CNV), are responsible for the majority of vision loss associated with AMD¹. Prior to the advent of intravitreal anti-vascular endothelial growth factor (VEGF) injections, effective treatment options for neovascular AMD (nAMD) were limited^{2,3}. Anti-VEGF agents have revolutionized nAMD treatment by not only preserving, but also potentially restoring visual function in many patients⁴. Treatment duration effect, however, remains somewhat variable and frequent office visits for surveillance and treatment are often necessary. This places a major burden not only on patients, but caregivers, physicians, and the health care system as well. Retina specialists are now faced with the challenge of maximizing visual outcomes, while minimizing treatment burden and treatment-related complications.

Several studies have explored other treatment modalities that may augment and possibly extend the effect of intravitreal anti-VEGF injections in order to mitigate the heavy burden they pose⁵⁻⁷. Various pathophysiologic mechanisms to reduce treatment burden have been proposed, including inflammatory mediators, components of the renin-angiotensin system, and beta-adrenergic blockade⁵⁻⁷. Studies in murine models revealed that beta-adrenergic blockade reduced expression of VEGF and induced regression of CNV⁷. A recent retrospective study did not reveal a protective effect of BB use between matched subjects with neovascular and non-neovascular AMD⁸. While this study offered evidence that BBs do not prevent the initiation of CNV, it did not investigate the findings established by the murine models, namely its role in inducing regression of CNV^{7,8}. A report by Montero *et al.*⁹ gave clinical credence to the theory of augmented CNV regression by reporting that over a 2-year period, patients on systemic beta-blockers (BB) received an average of 5.2 (SD=2.4) anti-VEGF injections compared to 7.9 (SD=3.4) in those who were not on BBs. The study was a small case series of 46 eyes that used patient self-report of concomitant systemic medications to evaluate a differential in CNV response to treatment⁹. The limited sample size and lack of a refined control group makes the generalization of the study difficult, but its findings warrant additional investigation. The aim of this study is to use a large national insurance claims database to determine whether oral beta-adrenergic blocking agents decrease the number of intravitreal injections in patients with incident nAMD.

Methods

Data Set

The Clinformatics™ Data Mart Database (OptumInsight, Eden Prairie, MN) contains de-identified medical claims of beneficiaries from a large insurance network in the United States. The database contains all outpatient medical claims, claim-associated diagnoses, pharmaceutical prescriptions filled, and demographic data of beneficiaries during their enrollment in the insurance plan. The subset data of interest for this study included all patients diagnosed with nAMD on or after July 2006 to December 2013. The University of Pennsylvania's Institutional Review Board declared this study exempt from review due to the de-identified nature of the data.

Subjects

Beneficiaries greater than or equal to 60 years of age with a new diagnosis of nAMD and at least one anti-VEGF injection were identified. The index date was considered the date of the incident diagnosis. Two cohorts were created for comparison consisting of patients with regular use of BBs or calcium channel blockers (CCB), defined as at least 80% daily coverage for a prescription in the respective class of medication during the observation period and no more than 30 days between refills. The number of intravitreal injections administered to each group was then evaluated after a 1-year observation period following the index date. CCBs were chosen as the comparison group because they have similar medical indications as BBs, but are not known to have any influence on VEGF levels or CNV growth. Exclusion criteria included a previous diagnosis of a disease that could lead to anti-VEGF use (cystoid macular edema, diabetic retinopathy, retinal vein occlusion, or sickle cell), less than 2 years of data prior to the index date, less than one year of data after the index date, or use of the other class of medication during the observation period (including topical BB use in the CCB group).

Main Outcome Measures

The primary outcome of interest was the difference in the mean number of intravitreal injections administered between the two cohorts. Covariates of interest included age, gender, race, year of diagnosis, and associated systemic diseases (history of diabetes mellitus, chronic kidney disease, transient ischemic attack, ischemic heart disease, chronic pulmonary disease, chronic liver disease, peripheral vascular disease, any malignancy, acute venous thrombosis, pulmonary embolism, atrial fibrillation, atrial flutter, chronic heart failure, and acute myocardial infarction). See Table 1 for complete list of *ICD-9* codes used during this study.

Statistical Analysis

Demographic characteristics were obtained at the index date and analyzed using means and standard deviations for continuous variables and frequencies and percentages for categorical variables. Student t-tests were used for comparisons of continuous variables and chi-squared tests were used for categorical variables. An independent two-sample t-test was performed for the unadjusted comparison of the mean number of intravitreal injections between the two cohorts and a multiple linear regression was performed for the covariate-adjusted comparison. Statistical analysis was performed using SAS (version 9.4; SAS Institute Inc., Cary, NC).

Results

After inclusion and exclusion criteria, a total of 394 subjects remained for analysis (Figure 1), which consisted of 239 subjects in the BB group and 155 subjects in the CCB group. The majority of subjects in both groups were female (63.6% BB and 62.6% CCB; $p=0.84$), white (87.9% BB and 80.0% CCB; $p=0.09$), and older in age (78.0; SD=6.2 BB and 78.0; SD=5.9 CCB; $p=0.94$). Common associated systemic diseases other than hypertension in each group were an arrhythmia (44.3% BB and 33.6% CCB; $p=0.03$), chronic pulmonary disease

(41.8% BB and 41.3% CCB; $p=0.91$), and diabetes (30.96% BB and 29.7% CCB; $p=0.79$). (See Table 2 for full list of baseline characteristics by cohort).

Univariate analysis revealed that the mean number of injections in the BB group was 6.43 (95% CI 5.90-6.95) versus 6.55 (95% CI 5.85-7.25) in the CCB group, for a mean difference of 0.12 less in the BB cohort (95% CI -0.98-0.74; $p=0.78$). After multivariate adjustment, the mean number of injections in the BB group was 6.32 (95% CI 5.77-6.87) versus 6.71 (95% CI 6.02-7.40) in the CCB group. The overall mean difference in injections between the two groups was again 0.39 less in the BB cohort (95% CI -1.29-0.51; $p=0.40$). In multivariate model testing the only disease history that was significantly associated with the number of injections was a history of transient ischemic attack ($p<0.01$). All other associations tested were not statistically significant ($p>0.05$).

Discussion

Intravitreal anti-VEGF therapy has shifted the therapeutic paradigm for nAMD⁴. What was once considered a blinding disease with minimal treatment options for visual rehabilitation has now become a treatable chronic condition. However, significant variability in treatment response continues to pose a major challenge. Reasons for this variability have been attributed to tachyphylaxis, genetic differences, and concurrent topical or systemic medications⁹⁻¹². Unfortunately for our patients, many of these theories often do not stand up to rigorous clinical inquiry. This study did not find oral BB use to be associated with a decreased number of intravitreal anti-VEGF injections in incident nAMD patients.

Although several basic science and animal studies have argued for a role of BBs in CNV response⁵⁻⁷, the few existing human studies have displayed contradictory results^{8, 9, 13, 14}. First, the findings from the Beaver Dam Eye study¹⁴ and Thomas *et al.*⁸ argued against a protective effect of oral BB use in developing CNV. They postulated that this discrepancy between human response and animal models may be secondary to higher medication doses and alternate routes of administration in animals⁸. Next, findings in a small prospective interventional study suggested that topical dorzolamide-timolol administered as adjuvant therapy improved treatment response in nAMD subjects with incomplete response to intravitreal anti-VEGF injections¹³. The exact pathophysiology for this response is not clear, but may include its potent aqueous suppressant properties, which would theoretically increase the injected anti-VEGF's half-life, prolonging its length of action in the eye¹³. The effect of the individual drug components also cannot be ignored. The authors theorize that topical BBs may result in higher intraocular concentrations than oral formulations, improving ocular bioavailability and potentially enhancing its effect¹³.

Finally, Montero *et al.*⁹ demonstrated that those taking BBs were found to have received 2.7 less injections over roughly 2 years compared to non-users. Several differences exist between that study and the current study, which may explain the contradicting results. First, and likely most pertinent, the previous study used a control group made up of non-users of BBs. This may have introduced an indication bias into their study, in which the results being attributed to the BBs were actually due to the underlying indications for the BB usage. Our study attempted to address this bias by selecting a comparator medication class with similar

disease indications for use. Additionally, we further controlled for many of these medical indications beyond just hypertension in the multivariate analysis. Lastly, despite 2 years of treatment, the BB group in the previous study only received 5.5 bevacizumab injections. This is far less than the 14.1 average seen over 2 years in the *pro re nata* (PRN) bevacizumab arm of the Comparison of AMD Treatments Trials (CATT), suggesting that there may be some underlying differences in the study population compared to other nAMD patients¹⁵.

In addition to those already mentioned, several other strengths to our study exist. The patients for this study were drawn from a database that is comprised of all beneficiaries enrolled in a large national insurance network in the United States, not those simply treated by one physician or office. This, in addition to the availability of sociodemographic and detailed medical claims data, allowed us to control for multiple potentially confounding variables yet still maintain a meaningful sample size. Furthermore, pharmacy records rather than patient report determined medication usage, eliminating any component of recall bias.

Several study limitations should also be noted. First, we are unable to identify recommended treatment patterns based on claims data (i.e. monthly, PRN, or treat and extend). However, in order for this limitation to impact the reported results, these patterns would have needed to be different based on BB or CCB usage, which is unlikely to have occurred. Also, to further control for potential changes in types of treatment patterns over time, we included year of diagnosis into the model, which showed no association with number of injections. Next, despite the national cohort used to find study patients, the database consists of beneficiaries from one insurance network, which may not generalize to other patient populations. Additionally, diagnoses were based purely on *ICD-9* codes from medical claims data and are unable to be confirmed by review of medical records. Furthermore, the drug cohorts were chosen carefully for their similar medical indications of use, but the exact indication for the BB or CCB use could not be identified from the database. Similarly, this study abstracted diagnoses by patient and not individual eye, meaning an exact number of patients receiving bilateral treatment was unable to be calculated. This limitation would only have impacted the outcome if significantly more BB patients had bilateral disease than CCB patients, which although possible, is unlikely. Also, our study only examined 1 year of injections. It is possible that with a longer duration of observation a differential effect in medication class could be seen. Finally, we assume medication compliance based on pharmacy data and prescription refill dates, but this cannot be further verified.

With the large number of patients and injections included in the study we had an 80% power to detect an effect difference of 1.1 injections between the two study cohorts, which our data clearly did not demonstrate. Although our study was not powered to detect smaller differences, an argument could be made that any effect that reduces injections by less than 1 injection per year is not likely to be clinically significant, even if a higher powered study could find a statistically significant difference.

In conclusion, this study did not find a difference in the mean number of intravitreal anti-VEGF injections administered to incident nAMD subjects taking either oral beta- or calcium channel blockers over a 1-year observation period. Additional studies are warranted to

investigate other modifiable differences that may contribute to response variations in patients receiving anti-VEGF injections for nAMD.

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Figure 1.

Flow chart demonstrating the number of patients excluded at each criteria and the final inclusion cohort used for the study.

Table 1
ICD-9 Codes Used in the Study

Diagnosis	ICD-9 Code
Neovascular AMD	362.52
Macular edema	362.07, 362.53, 362.82, 362.83
Proliferative retinopathy	362.01, 362.02, 362.15, 362.16, 362.29, 364.42, 365.63, 365.89
Sickle cell disease	282.6
Other retinopathies	362.2x
Vein occlusion	362.3x
Diabetes mellitus	250.xx
Hypertension	401.xx, 402.xx-405.xx
Chronic kidney disease	582.xx, 583.xx, 585.1-585.4, 585.9, 586.xx, 587, 588.0
Ischemic stroke/transient ischemic attack	433.x1, 434.x1, 435, 436
Ischemic heart disease	421, 430
Chronic liver disease	456.0, 456.1, 456.2x, 572.2-572.8
Chronic pulmonary disease	416.8, 416.9, 490.x-505.x, 506.4, 508.1, 508.8
Peripheral vascular disease	093.0, 437.3, 440.x, 441.x, 443.1-443.9, 447.1, 557.1, 557.9, v43.4
Malignancy	140.x-172.x, 174.x-208.x, 238.6
Acute venous thrombosis	451.1x, 451.2, 451.81, 451.9, 453.1, 453.2, 453.4x, 453.6, 453.9 451.82, 451.83, 451.84, 451.89, 453.8x
Pulmonary embolism	415.11, 415.12, 415.13, 415.19
Atrial fibrillation	427.31
Atrial flutter	427.32
Congestive heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4-425.9, 428.xx
Myocardial infarction	410.xx, 411.xx, 412.xx
Arrhythmia	427.xx

Table 2
Baseline Characteristics of Cohorts

Characteristic	Beta-Blocker (n = 239)	Calcium Channel Blocker (n = 155)	P-Value
Age, mean (IQR)	78 (75 – 82)	78 (75 – 82)	0.94
	n (%)	n (%)	
Female	152 (63.6)	97 (62.6)	0.84
Race			0.09
White	210 (87.9)	124 (80.0)	
Black	6 (2.5)	10 (6.45)	
Hispanic	7 (2.9)	10 (6.45)	
Asian	3 (1.3)	4 (2.6)	
Other/unknown	13 (5.4)	7 (4.5)	
Hypertension	230 (96.2)	151 (97.4)	0.52
Diabetes mellitus	74 (30.96)	46 (29.7)	0.79
Chronic kidney disease	47 (19.7)	25 (16.1)	0.75
Transient ischemic attack	36 (15.1)	37 (23.9)	0.03
Ischemic heart disease	2 (0.84)	4 (2.6)	0.17
Chronic liver disease	6 (2.5)	0 (0)	0.05
Chronic pulmonary disease	100 (41.8)	64 (41.3)	0.91
Peripheral vascular disease	70 (29.3)	46 (29.7)	0.93
Malignancy	44 (18.4)	32 (20.7)	0.66
Acute venous thrombosis	29 (12.1)	14 (9.0)	0.88
Pulmonary embolism	5 (2.1)	2 (1.3)	0.56
Atrial fibrillation	70 (29.3)	38 (24.5)	0.30
Atrial flutter	13 (5.4)	8 (5.2)	0.90
Congestive heart failure	71 (29.7)	28 (18.1)	0.01
Myocardial infarction	54 (22.6)	21 (13.6)	0.03
Arrhythmia	106 (44.3)	52 (33.6)	0.03