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Ocular complications after anti-vascular endothelial growth factor therapy in Medicare patients with age-related macular degeneration

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Abstract

Purpose—To determine longitudinal rates of ocular complications after anti-vascular endothelial growth factor (VEGF) treatment for neovascular age-related macular degeneration (AMD) in a nationally representative longitudinal sample.

Design—retrospective, longitudinal case-control study.

Methods—Using the Medicare 5% claims database, diagnoses of neovascular AMD and anti-VEGF injections of ranibizumab, bevacizumab, or pegaptanib were identified from International Classification of Diseases (ICD-9-CM) and Current Procedural Terminology (CPT) procedure codes. 6,154 individuals undergoing anti-VEGF treatment for neovascular AMD (total of 40,903 injections) were compared with 6,154 matched controls with neovascular AMD who did not undergo anti-VEGF treatment. Propensity score matching was used to match individuals receiving anti-VEGF injections with controls. Rates of post-injection adverse outcomes (endophthalmitis, rhegmatogenous retinal detachment, retinal tear, uveitis, and vitreous hemorrhage) were analyzed by cumulative incidence and Cox proportional hazards model to control for demographic factors and ocular comorbidities.

Results—At 2-year follow-up, the rates of endophthalmitis per injection (0.09%; $p<0.01$), uveitis (0.11%; $p<0.01$), and vitreous hemorrhage per injection (0.23%; $p<0.01$) were significantly higher in the anti-VEGF treatment group. With Cox proportional hazards modeling, the anti-VEGF

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treatment group had an 102% higher risk of severe ocular complications overall, and a 4% increased risk per injection, both of which were statistically significant ($p<0.01$)

Conclusions—Rates of endophthalmitis, uveitis, and vitreous hemorrhage were higher in the group treated with anti-VEGF injection than in the control group, though nevertheless rare in both groups. The overall risk of severe ocular complications was significantly higher in the anti-VEGF treatment group.

Introduction

Age-related macular degeneration (AMD) is the leading cause of blindness in developed countries and the third leading cause of blindness worldwide.[1–3] Since 2005, the advent and widespread use of anti-vascular endothelial growth factor (VEGF) drugs for the treatment of neovascular AMD has dramatically changed the management of this disease.[4–5] While the visual prognosis for these patients has improved, each intravitreal injection poses a risk of infection, post-injection inflammation, retinal tear or detachment, and vitreous hemorrhage.

The three medications delivered via intravitreal injection for treatment of neovascular AMD are ranibizumab (Lucentis; Genentech, South San Francisco, California, USA), bevacizumab (Avastin; Genentech), and pegaptinib (Macugen; OSI-Eyetech, New York, New York, USA). Ranibizumab and pegaptanib have been FDA approved for treatment of neovascular AMD, and bevacizumab has been used off-label for this indication with increasing frequency.[6–7] A review of safety data from 4 randomized trials of ranibizumab (MARINA, ANCHOR, SAILOR, and PIER) where 3,252 patients received > 28,500 injections found a 0.05% rate of endophthalmitis per injection (Boyer DS et al. A Safety Overview of Ranibizumab in Patients With Wet AMD: ANCHOR, MARINA, PIER, and SAILOR Studies. Abstract PO247 presented at the AAO/SOE Joint Annual Meeting, 8–11 November 2008, Atlanta.) Retrospective reviews looking at bevacizumab, pegaptinib, and ranibizumab have found rates of endophthalmitis per injection of 0%, 0.02%, 0.077%, and 0.16%.[8–11] Rates of serious intraocular inflammation have ranged widely from 0.03% per injection in the 4 randomized trials of ranibizumab,[12] to 0.09% in a 12-month study of bevacizumab,[13] to 1.5% in a retrospective review of ranibizumab and bevacizumab injections.[8] Rates of mild or moderate intraocular inflammation have been much higher, occurring in up to 17.1% of patients in the ANCHOR study.[5] Retinal tear and retinal detachment have been rare in published studies to date; the rate of retinal detachment was 0% in the MARINA trial, 0.03% in the ANCHOR study, and 0.16% in a retrospective review of bevacizumab injections.[4–5, 13]

To date, the ocular complications of intravitreal injections have not been studied in the Medicare population. This study examines the ocular complications of anti-VEGF injections given for neovascular AMD in a nationally representative longitudinal cohort of elderly persons. This represents the largest reported sample studying ocular complications of patients undergoing anti-VEGF treatment, and offers the advantage of reducing surgeon- and center-specific factors.

Methods

Data

For this retrospective, longitudinal cohort analysis, Medicare 5% inpatient, outpatient, Part-B, and durable medical equipment claims files were used to identify a nationally representative sample of Medicare beneficiaries aged 68+ years diagnosed with neovascular AMD. The data contained information on beneficiaries' demographic characteristics, diagnoses (International Classification of Diseases, 9th Revision, Clinical Modification,

ICD-9-CM), procedure codes (Current Procedural Terminology, CPT-4; Healthcare Common Procedure Coding System, HCPCS), and U.S. Centers for Medicare and Medicaid Services (CMS) provider physician specialties, submitted with claims which were used to identify whether or not an individual received anti-VEGF treatment and related adverse outcomes, and to ensure individuals had seen an eye specialist. Data were linked by a unique identifier, permitting construction of longitudinal, person-specific data from January 1, 2002 through December 31, 2008.

Sample Selection

Individuals undergoing anti-VEGF treatment between 2005 and 2008 were identified using these codes: pegaptanib (HCPCS: J3490, C9128, J2503), bevacizumab (J3490, J3590, J9035), and ranibizumab (J3490, J3590, C9399, and C9233). For the unclassified codes (J3490, J3590, C9399), price ranges and eye injection codes on day of treatment were jointly used to ascertain those who were receiving anti-VEGF treatments and those who were not. The specific price ranges were pegaptanib ($750–$1000), bevacizumab ($1–$200) and ranibizumab ($1500 – $2500).

We employed a 3-year look-back period to identify co-morbid eye conditions and to ensure that the individuals receiving anti-VEGF had at least two previous diagnoses of neovascular AMD (ICD-9 codes: 362.52, 362.42, 362.43) before anti-VEGF treatment. To ensure that we had a full 3-year look-back, individuals under age 68 were excluded from our sample, as were individuals who were enrolled in an HMO or who lived outside the United States for more than 12 months during the 3 year look-back period. Baseline date for individuals in the anti-VEGF group was the first date they received an anti-VEGF injection.

The control group was composed of individuals who had received at least two diagnoses of neovascular AMD within a 3 year look back from 01/01/2006 and had not received any anti-VEGF treatments up until the end of our study period, 12/31/2008. The same age, HMO, and living outside the U.S. restrictions were applied to the control group. Baseline date was January 1, 2006 for the control sample. We further required individuals in the control group to have at least 1 visit to an ophthalmologist (CMS code: 18) or optometrist (41) during the follow-up period.

We followed individuals for 730 days or until they developed an eye complication or until they were censored. Censoring occurred when a beneficiary underwent cataract or glaucoma surgery, joined a HMO, moved outside of the US, or died during the follow-up period.

Adverse Events

Adverse events were endophthalmitis (ICD-9-CM: 360.0), rhegmatogenous retinal detachment (361.0), retinal tear (361.30–.31), uveitis (364.00–.05, 364.10–.11), and vitreous hemorrhage (379.23). These diagnosis codes were grouped together to form a severe ocular complications category. We required that control and treatment persons never received a prior diagnosis of endophthalmitis, rhegmatogenous retinal detachment, retinal tear, uveitis, and vitreous hemorrhage before their date of first anti-VEGF treatment if they were in the treatment or 01/01/2006 if they were in the control group. We also did not include any adverse events if they occurred after cataract or glaucoma surgery during the follow-up period.

Propensity Score Matching

In the first step of the matching process, we performed logit analysis to predict the probability of an individual undergoing anti-VEGF treatments. Covariates for the logit

analysis were binary variables for gender, dry AMD, black race, other race, and continuous variables for age and Charlson index, a widely-used measure of comorbidity.[14]

In the second step of the matching process, we paired an individual undergoing anti-VEGF treatment to his or her nearest match in the control group using the predicted probability of an anti-VEGF treatment from the logit analysis. Propensity score matching reduces selection bias in the receipt of anti-VEGF treatments among individuals with neovascular AMD.[15–16] The program, SAS Greedy 5 to 1 digit match macro (by Lori S. Parsons, accessed April 20, 2009, at http://www2.sas.com/proceedings/sugi26/p214-26.pdf) made the best match first by pairing individuals in the treatment and control group on exact 5 digit matches of their predicted probability of receipt of anti-VEGF treatments. Considering all persons not previously matched the macro then attempted to match individuals based on 4 digits of their propensity score, then 3, then 2, and 1. Individuals unable to be matched on 1 digit were excluded. Standardized differences were calculated for the matched sample and revealed no differences >10%, resulting in a well-matched sample.[17–18]

Analysis

Time to event analysis was performed on the resulting matched sample using a Cox proportional hazards model. Unadjusted and adjusted time to a severe ocular complication was studied. We performed 4 specifications: (1) Having a complication using a binary indicator for anti-VEGF treatment *unadjusted* for other covariates. (2) Having a complication using a binary indicator for anti-VEGF treatment *adjusted* for other covariates. The adjusted model consisted of controls for age, background diabetic retinopathy, proliferative diabetic retinopathy, Alzheimer's or other dementia, cataract surgery, cataract, glaucoma, glaucoma surgery, male gender, white race, Charlson index, dry AMD, blindness/low vision and duration of neovascular AMD. (3) Having a complication based on the frequency of anti-VEGF treatment *unadjusted* for other covariates and (4) Having a complication based on the frequency of anti-VEGF treatment *adjusted* for other covariates. The Duke University Institutional Review Board approved this study.

Results

During the study time period, there were 2,163,207 beneficiaries in the Medicare 5% inpatient, outpatient, Part-B, and durable medical equipment claims files. Of these beneficiaries, 20,671 individuals (1.0% of the total) with a diagnosis of neovascular AMD between 2005–2008 were identified who met the inclusion criteria outlined in the Methods section. 96.4% of the diagnoses came from ophthalmologist examinations, and 3% of the data came from optometrist examinations. Of the 20,671 individuals with neovascular AMD, 6,154 (29.8%) underwent at least one anti-VEGF injection during the study time period, receiving a total of 40,903 injections. Individuals were followed for 2 years or until they developed an eye complication or until they were censored; mean follow-up time was 533 days for the control group and 435 days for the anti-VEGF treatment group. Beneficiaries were censored if they underwent cataract or glaucoma surgery during the follow-up period, joined an HMO, moved outside the US, or died; 35 beneficiaries were censored in the control group and 72 patients were censored in the anti-VEGF treatment group.

In order to reduce selection bias, propensity score matching was then performed with the covariates of gender, race, age, history of dry AMD, and the Charlson co-morbidity index to create a control group of 6,154 individuals who had neovascular AMD but did not undergo an anti-VEGF injection during this time period. In terms of the matched characteristics of age, gender, race, and mean value of the Charlson Index, the two groups were very similar (Table 1). For ocular co-morbidities, the control group was significantly more likely than the

anti-VEGF treatment group to have cataract (47% vs. 45%, p=0.03) and significantly less likely to have undergone previous cataract surgery (44% vs. 47%, p<0.01) or glaucoma surgery (4% vs. 6%, p<0.01).

Between 2005–2008, the number of all types of anti-VEGF injections in the sample increased from 3,393 in 2005 to 15,103 in 2008, and the number of bevacizumab and ranibizumab injections increased dramatically (Table 2). By 2008, bevacizumab injections comprised 54.5% of anti-VEGF injections overall. The number of pegaptanib injections declined precipitously, from 96.4% of anti-VEGF injections in 2005 to only 1.1% of injections by 2008.

In terms of serious ocular complications, there were 38 cases of endophthalmitis in the anti-VEGF treatment group between 2005–2008, compared to only 6 cases in the control group (Table 3). Uveitis was significantly more common in the anti-VEGF treatment group (0.73% vs. 0.37%, p< 0.01). Vitreous hemorrhage was also significantly more common in the anti-VEGF treatment group (1.80% vs. 0.94%, p<0.01). There were no significant differences between the two groups in rates of rhegmatogenous retinal detachment or retinal tear. The rate of endophthalmitis per anti-VEGF injection was 0.09%; the rates of rhegmatogenous retinal detachment, retinal tear, uveitis, and vitreous hemorrhage per injection were also very low, ranging from 0.06% for retinal tear to 0.23% for vitreous hemorrhage. The rate of complication per injection in excess of the observed rate in the control group (the rate presumably attributable to anti-VEGF treatment alone) was 0.08% for endophthalmitis, 0.05% for uveitis, and 0.12% for vitreous hemorrhage.

Without adjusting for other covariates, individuals undergoing anti-VEGF treatment had a 104% higher risk of complication overall (HR: 2.036; 95% CI: 1.630, 2.544; Table 4). Adjusting for other covariates, the hazard ratio was essentially the same (HR: 2.017; 95% CI: 1.609, 2.528). The risk of complication for each anti-VEGF injection was about 4% in both the unadjusted (HR: 1.038; 95% CI: 1.025, 1.052) and adjusted (HR: 1.041; 95% CI: 1.027, 1.054) models.

A previous diagnosis of proliferative diabetic retinopathy more than doubled the risk of serious ocular complication (HR: 2.172; 95% CI: 1.103, 4.280). A previous history of glaucoma surgery also increased the risk of serious ocular complication by 70% (HR: 1.695; 95% CI: 1.115, 2.575).

Discussion

Anti-VEGF injections have dramatically altered treatment of neovascular AMD. Visual prognoses have improved, but treatment requires as frequent as monthly intravitreal injections with all of the accompanying risks of endophthalmitis, rhegmatogenous retinal detachment, retinal tear, uveitis, and vitreous hemorrhage. In spite of its promise for treating persons with neovascular AMD, only 6,154 (29.8%) of the 20,671 individuals diagnosed with neovascular AMD between 2005–2008 in the Medicare 5% sample underwent treatment with anti-VEGF injections. This could be due to the fact that coding of a diagnosis of neovascular AMD may reflect some prevalent cases with long-standing disease or disciform scars which are not amenable to anti-VEGF therapy. Other factors limiting treatment may be barriers in patient access to care or provider availability in certain geographic areas.

The endophthalmitis rate per anti-VEGF injection in a summary of major randomized trials was 0.05% and ranged from 0–0.16% in a series of retrospective studies.[8–12] The rate of endophthalmitis per injection was 0.09% in this study, which is higher than that reported for randomized controlled trials but comparable to rates reported in retrospective observational

studies. Given the diverse background of sites included in this study, this sample presumably encompasses a range of practices which have been reported such as unilateral injections, same-day bilateral injections, use of pre- and/or post-injection antibiotics, use of povidone iodine, and use of lid speculums.[19–20] The higher rate of endophthalmitis in this cohort compared to the randomized clinical trial data may be more representative of variations in patient populations and actual pre- and post-injection practices than data from clinical trials with rigorous prophylaxis protocols.

The study was not powered to detect differences between rates of endophthalmitis between different types of anti-VEGF treatments. The rates of endophthalmitis, uveitis, and vitreous hemorrhage were significantly higher in the anti-VEGF treatment group when compared to the matched control group, but the differences in rates of rhegmatogenous retinal detachment and retinal tear were not statistically significant. The difference in the rates of vitreous hemorrhage was likely not due to the presence of background or proliferative diabetic retinopathy; in fact the rates of background diabetic retinopathy and proliferative diabetic retinopathy were comparable in the two groups (Table 1). However, the anti-VEGF treatment group was probably more likely to have active choroidal neovascularization which may be responsible for the higher rates of vitreous hemorrhage in this group.

Even after controlling for demographic factors and other ocular comorbidities, anti-VEGF treatment was associated with a higher overall risk of ocular complications, with double the risk of serious ocular complication for those in the anti-VEGF treatment group, and 4.1% higher risk for each anti-VEGF treatment. However, ocular complications with anti-VEGF treatment are still quite rare and are actually lower than reported risks with other types of intravitreal injections.[21] A review of 1,739 intravitreal triamcinolone injections reported rates of endophthalmitis of 0.6% per injection.[21]

This study has several strengths. First, we used a large, nationally representative longitudinal sample of Medicare 5% inpatient, outpatient, Part-B, and durable medical equipment claims files. This cohort of 20,671 patients with neovascular AMD, of whom 6,154 received 40,903 anti-VEGF injections, represents the largest study of ocular complications of anti-VEGF treatment to date, and no other studies have used Medicare claims data to examine patterns in this particular patient population. Previous studies of the reliability and completeness of the Medicare claims database in other diseases have shown good agreement between claims data and medical records and clinical registries with kappa values between 0.69–0.90.[22–23] In addition, Javitt et al. found 99% accuracy of Medicare Part B coding for cataract surgery when compared with medical records.[24] This study complements the previously published literature which consists primarily of retrospective single-center case series, as well as a few multi-center prospective, randomized trials. The wide range of patients, clinical sites, and clinical practices make this study more generalizable to the care and outcomes received by the elderly population in the U.S. as a whole, and potentially relevant to the outcomes in elderly populations in developed countries worldwide.

A deficiency of insurance claims is that the data collected are for billing purposes and do not contain detailed clinical information, such as the exact level of intraocular inflammation. Some studies have reported cases of “pseudo-endophthalmitis” with culture-negative severe intraocular inflammation that is felt to be a reaction to a non-infectious substance, similar to toxic anterior segment syndrome (TASS).[25] These cases would be difficult to distinguish in this cohort since culture results and the level of intraocular inflammation are not available. In addition, while we can identify beneficiaries with a diagnosis of neovascular AMD via Medicare billing data, more details regarding the activity and location of the choroidal neovascularization are not available. Therefore, the Medicare beneficiaries who did not receive anti-VEGF treatment were possibly more likely to have inactive disease, disciform

scars, or extramacular choroidal neovascularization than those in the anti-VEGF treatment group. Lastly, insurance claims data do not distinguish between the eye undergoing anti-VEGF treatment and the eye with subsequent complications; however, by censoring beneficiaries after they undergo cataract or glaucoma surgery during the study period, we hope to reduce the number of cases of endophthalmitis which could be attributable to other causes.

In summary, using a nationally representative longitudinal sample of individuals undergoing anti-VEGF treatment for neovascular AMD, we found a higher risk of endophthalmitis per injection in this study (0.09% or approximately 1 case per 1111 injections) compared to the rate reported in randomized, clinical trials (0.05% or 1 case per 2000 injections). The risk of ocular complications was also significantly higher for persons undergoing anti-VEGF injection when compared to persons with neovascular AMD who did not receive anti-VEGF treatment. The results of this study reflect actual practice patterns at clinical sites across the country rather than controlled study environments.

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Table 1

Baseline characteristics of matched control and anti-vascular endothelial growth factor (VEGF) treatment groups.

Baseline demographic characteristics	**Control group (n=6154)**	**Anti-VEGF treatment group (n=6154)**	**p-value**
Age (years)	82.23	82.15	0.0235
% Male	32%	32%	0.6882
% Black	1%	1%	0.631
Charlson Index (0–18)	1.92	1.91	0.6091
Baseline ocular Characteristics	**Control group (n=6154)** Number (%)	**Anti-VEGF treatment group (n=6154)** Number (%)	**p-value**
Background diabetic retinopathy	357(6%)	318(5%)	0.114
Proliferative diabetic retinopathy	75(1.2%)	90(1.5%)	0.2401
Cataract	**2868(47%)**	**2746(45%)**	**0.0258***
Cataract surgery	**2701(44%)**	**2866(47%)**	**<.01****
Glaucoma	1833(30%)	1762(29%)	0.1582
Glaucoma surgery	**251(4%)**	**380(6%)**	**<.01****

* difference significant at the p≤0.05 level

** difference significant at the p<0.01 level

Table 2

Types of anti-VEGF intravitreal injection by year

Year	Bevacizumab Number (%)	Ranibizumab Number (%)	Pegaptanib Number (%)	Total Number
2005	116(3.42%)	5(0.15%)	3272(96.43%)	3393
2006	3326(40.91%)	2807(34.52%)	1998(24.57%)	8131
2007	6814(47.73%)	7187(50.34%)	275(1.93%)	14276
2008	8235(54.53%)	6704(44.39%)	164(1.09%)	15103

Table 3

Ocular complications after anti-VEGF treatment for neovascular AMD.

Ocular complication	Control group (n=6154 pts) Number (%)	Anti-VEGF treatment group (n=6154 pts) Number (%)	p-value	Rate of complication per injection in treatment group (n=40903 injections) %	Rate of complication per injection in treatment group in excess of observed rate in control group (n=40903 injections) %
Endophthalmitis	**6(0.10%)**	**38(0.62%)**	**<.01****	0.09%	0.08%
Rhegmatogenous retinal detachment	40(0.65%)	41(0.67%)	0.9115	0.10%	0.002%
Retinal tear	17(0.28%)	24(0.39%)	0.2743	0.06%	0.02%
Uveitis	**23(0.37%)**	**45(0.73%)**	**<.01****	0.11%	0.05%
Vitreous hemorrhage	**46(0.75%)**	**95(1.54%)**	**<.01****	0.23%	0.12%

* difference significant at the p≤0.05 level

** difference significant at the p< 0.01 level

Table 4

Cox proportional hazards model predicting time to severe ocular complications after anti-VEGF treatment for neovascular AMD.

	Any anti-vascular endothelial growth factor (VEGF) injection		Per anti-VEGF injection	
Covariates	**Unadjusted Hazard ratio (95% CI)**	**Adjusted Hazard ratio (95% CI)**	**Unadjusted Hazard ratio (95% CI)**	**Adjusted Hazard ratio (95% CI)**
VEGF treatment	**2.036 (1.630, 2.544)** **	**2.017 (1.609, 2.528)** **		
Number of VEGF treatments			**1.038 (1.025, 1.052)** **	**1.041 (1.027, 1.054)** **
Baseline ocular characteristics				
Background diabetic retinopathy		1.007 (0.626, 1.622)		1.011 (0.629, 1.625)
Proliferative diabetic retinopathy		**2.172 (1.103, 4.280)***		**2.175 (1.107, 4.272)***
Cataract		1.134 (0.898, 1.434)		1.126 (0.891, 1.423)
Cataract surgery		1.127 (0.889, 1.430)		1.137 (0.896, 1.443)
Glaucoma		1.105 (0.868, 1.405)		1.092 (0.859, 1.389)
Glaucoma surgery		**1.695 (1.115, 2.575)** *		**1.626 (1.067, 2.478)***
Had dry AMD prior to neovascular AMD		0.979 (0.713, 1.344)		0.967 (0.705, 1.327)
Blindness/low vision		0.979 (0.695, 1.379)		1.006 (0.714, 1.417)
Year of neovascular AMD diagnosis		0.99 (0.966, 1.036)		1.012 (0.977, 1.048)
Demographic characteristics				
Age		0.991 (0.973, 1.009)		0.993 (0.975, 1.011)
Male		1.244 (0.995, 1.555)		1.237 (0.990, 1.547)
White		1.615 (0.667, 3.915)		1.596 (0.658, 3.867)
Alzheimer's or other dementia		1.053 (0.677, 1.637)		1.044 (0.671, 1.624)
Charlson Index		1.031 (0.980, 1.085)		1.035 (0.984, 1.089)

* difference significant at the 5% level

** difference significant at the 1% level

Severe ocular complications include endophthalmitis, rhegmatogenous retinal detachment, retinal tear, uveitis, and vitreous hemorrhage.