AMERICAN ACADEMY™
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Trends of Anti-Vascular Endothelial Growth Factor Use in Ophthalmology Among Privately Insured and Medicare Advantage Patients

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Purpose: To characterize the first 10 years of intravitreal anti-vascular endothelial growth factor (VEGF) medication use for ophthalmic disease, including bevacizumab, ranibizumab, and aflibercept.

Design: A retrospective cohort study using administrative claims data from January 1, 2006 to December 31, 2015.

Subjects: Total of 124 835 patients 18 years of age or over in the United States.

Methods: OptumLabs Data Warehouse, which includes administrative claims data for over 100 million commercially insured and Medicare Advantage individuals, was used to identify patients receiving intravitreal anti-VEGF injections based on Current Procedural Terminology codes.

Main Outcome Measures: Total and annual numbers of intravitreal anti-VEGF injections, as well as injections per 1000 enrolled patients per general category of ophthalmic disease, overall and for each available medication.

Results: There were 959 945 anti-VEGF injections among 124 835 patients from 2006 to 2015. Among all injections, 64.6% were of bevacizumab, 22.0% ranibizumab, and 13.4% aflibercept; 62.7% were performed to treat age-related macular degeneration (AMD), 16.1% to treat diabetic retinal diseases (including 0.9% of all injections that were for proliferative diabetic retinopathy), 8.3% to treat retinal vein occlusions, and 12.9% for all other uses. Use of bevacizumab and ranibizumab for AMD plateaued as of 2011/2012 and decreased thereafter (in 2006, 58.8 and 35.3 injections/1000 AMD patients, respectively; in 2015, 294.4 and 100.7 injections/1000), whereas use of aflibercept increased (1.1 injections/1000 AMD patients in 2011 to 183.0 injections/1000 in 2015). Bevacizumab use increased each year for diabetic retinal disease (2.4 injections/1000 patients with diabetic retinal disease in 2009 to 13.6 per 1000 in 2015) while that of ranibizumab initially increased significantly and then declined after 2014 (0.1 in 2009 to 4.0 in 2015). Aflibercept use increased each year in patients with diabetic retinal diseases and retinal vein occlusions (both $<$0.1 per 1000 retinal vein occlusion patients in 2011, 5.6 and 140.2 in 2015).

Conclusions: Intravitreal injections of anti-VEGF medications increased annually from 2006 to 2015. Bevacizumab was the most common medication used, despite its lacking U.S. Food and Drug Administration approval to treat ophthalmic disease, and AMD was the most common condition treated. Ranibizumab use declined after 2014 while both the absolute and relative use of bevacizumab and aflibercept increased. *Ophthalmology 2016;■:1–8 © 2016 by the American Academy of Ophthalmology*

Intravitreal anti–vascular endothelial growth factor (anti-VEGF) drugs have revolutionized the practice of ophthalmology.[1] Although the first anti-VEGF drug, bevacizumab (Avastin; Genentech South San Francisco CA), was approved for use by the U.S. Food and Drug Administration (FDA) in 2004 for the treatment of metastatic carcinoma of the colon or rectum,[2] ranibizumab (Lucentis; Genentech) was approved soon thereafter in 2006 for the treatment of neovascular age-related macular degeneration (AMD). Ophthalmologists quickly determined that bevacizumab was also efficacious for the treatment of neovascular AMD, and that repackaging of the medication at the appropriate dosage for ophthalmic treatment would allow physicians to administer many treatments from a single oncologic dose vial at relatively low cost.[3] In 2011, another anti-VEGF drug, aflibercept (Eylea; Regeneron, Tarrytown, NY) was approved for use by the FDA.[4]

Ranibizumab and aflibercept are currently FDA approved for the treatment of neovascular AMD, diabetic macular edema (DME), diabetic retinopathy (DR) associated with DME, and macular edema secondary to retinal vein occlusion (RVO). Although bevacizumab remains "off label" for purposes of treating ophthalmic disease, it is estimated that ophthalmologists used the medication to treat 51 different

http://dx.doi.org/10.1016/j.ophtha.2016.10.036
ISSN 0161-6420/16

ocular conditions as of the end of the last decade.[5] Ranibizumab and aflibercept are also used off label for non-FDA-approved ophthalmic conditions, but to a lesser extent, possibly owing to financial considerations.

Despite the lack of FDA approval for ophthalmic disease, data suggest that bevacizumab has a similar efficacy as ranibizumab for the treatment of neovascular AMD. The 2011 publication of the Comparison of Age-Related Macular Degeneration Treatments Trials reported that patients receiving either bevacizumab or ranibizumab had "equivalent effects on visual acuity" at 1 and 2 years.[6,7] For treatment of DME, the data are less clear. The recent major trial by the Diabetic Retinopathy Clinical Research Network (DRCR.net) comparing all 3 medications (Protocol T) found that, for patients with worse presenting visual acuities, aflibercept was superior to bevacizumab and ranibizumab at 1 year, but that at 2 years aflibercept was superior to bevacizumab, with ranibizumab statistically similar to both medications.[8]

While debate continues regarding the relative effectiveness of anti-VEGF medications for treatment of ophthalmic disease, an important consideration is the substantial discrepancy in drug prices per standard dose: aflibercept costs $1950 (2.0 mg/0.05 ml), and ranibizumab costs $1200 for DR−related indications (0.3 mg/0.05 ml) and $1950 for AMD and retinal venous occlusive disease (0.5 mg/0.05 ml), whereas repackaged bevacizumab costs only ∼$50 per 1.25-mg dose.[3,8,9] Given the numerous indications, the varied use, and the large differences in cost, our objective was to examine national patterns of anti-VEGF drug use for ophthalmic conditions, characterizing trends and demographic patterns of bevacizumab, aflibercept, and ranibizumab use from 2006 to 2015 among both privately insured and Medicare Advantage patients.

Methods

Data Source

We conducted a retrospective analysis using the OptumLabs Data Warehouse, a large U.S. database that includes administrative claims data from privately insured and Medicare Advantage enrollees.[10] The database is composed of administrative claims for more than 100 million individuals in all 50 states and of all ages and ethnic and racial groups.[11] Administrative claims include medical claims for professional (e.g., physician), facility (e.g., hospital), and pharmacy claims. Pursuant to the Health Insurance Portability and Accountability Act, the use of deidentified data does not require Institutional Review Board approval.

Study Sample

We identified all intravitreal injections with an associated anti-VEGF drug code on the same day between January 1, 2006 and December 31, 2015. To identify the study population, we first selected all claims for intravitreal injections using the Current Procedural Terminology code 67028. Anti-VEGF medications associated with intravitreal injections were identified using medication-specific Healthcare Common Procedure Coding System codes (bevacizumab, C9257, S0116, J9035, and Q2024; ranibizumab, J2778, C9233; aflibercept, J0178, Q2046, C9291). Because the introduction of Healthcare Common Procedure Coding System codes lag behind FDA approval and because bevacizumab lacks a code specific to ocular use, we also included claims for unclassified/miscellaneous drug codes administered on the same day as an injection (J3490, J3590, and C9399).[9] We assigned these claims to specific drugs using total paid amounts, since the costs differed significantly across drugs.[9] Total paid amounts capture the sum of the total amount paid by both the enrollee and health plan for the drug. We imputed the identification of unclassified drugs with amounts of <$200 as bevacizumab, and those with ≥$1200 as ranibizumab from July 2006 through 2010 and as aflibercept in 2011 through 2015, using methods that have been used in prior studies.[9,12] Medications under $200 that were coded as miscellaneous and were and not coded as another medication (i.e., triamcinolone, which is J3300) were characterized as bevacizumab depending on the time frame. In addition, we excluded all unclassified/miscellaneous records with allowed amounts of $200 to $1199, which may have indicated another treatment, such as pegaptanib. We restricted the analysis to enrollees who were 18 years or older and required that enrollees had medical coverage at the time of their injection.

Patient Characteristics

To understand the demographic and clinical characteristics of the patients receiving the injections, we used age, sex, race/ethnicity, and census region information and indicators for ocular conditions—AMD, diabetic retinal diseases, or RVO. Reasons for injections were identified using the primary International Classification of Diseases (ICD) Ninth Revision, Clinical Modification (ICD-9-CM) codes and categorized as being treated for AMD (ICD-9 codes 362.50, 362.51, and 362.52 as well as ICD, Tenth Revision [ICD-10] codes H3532, H3531, and H3530), diabetic retinal diseases (ICD-9 codes 250.50, 362.07, 362.02, 250.51, 250.52, 362.01, and 250.00, as well as ICD-10 codes E11351, E11331, E11341, E11311, E10351, E11359, E10331, E10341, E11329, E10359, E10321, E10311, E11339, E1139, E11349, E11319, E10329, E1039, E13321, E13351, E10339, E13359, E10349, E13341, E13349, and all other codes indicating diabetes with retinopathy), or RVO (ICD-9 codes 362.36 and 362.35, as well as ICD-10 codes H34831, H34832, H34812, H34811, E11321, H34813, H34833, H34819, H34839, H3412, H349); all other ICD-9 and ICD-10 codes were categorized as alternative use.

Statistical Analysis

We examined the rates of anti-VEGF characterized over time in the study population by drug and indication. Patient characteristics (age, sex, race, census region) were described using mean (standard deviation) or count (percentage) as appropriate. We calculated annual rates by using the number of anti-VEGF injections as the numerator and the total number of enrolled patients as the denominator. Furthermore, we assessed rates by indication for administration, using the number of anti-VEGF injections per indication as the numerator and per 1000 patients with the condition as the denominator. To ensure that the denominator has the same restrictions as the numerator, only beneficiaries with a primary condition of the following were included: AMD, diabetic eye disease, or RVO. Rates were expressed as the number of anti-VEGF injections per 1000 patients. This rate has been expressed in similar studies examining anti-VEGF drug use.[13] The authors defined per-patient use as injections per 1000 beneficiaries who were within a broad diagnosis category (i.e., AMD), not the overall pool of beneficiaries. All analyses were conducted using SAS software version 9.3 (SAS Institute Inc., Cary, NC).