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The use of bevacizumab and ranibizumab for branch retinal vein occlusion in medicare beneficiaries

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ABSTRACT

Purpose: To describe the frequency and variation of intravitreal bevacizumab and ranibizumab use for branch retinal vein occlusion (BVO) in the United States (US).

Methods: We obtained a 5% random sample of Medicare beneficiaries from the Medicare Denominator and Physician/Supplier Part B claims files from 2010 to 2013 and identified all beneficiaries with an ICD-9-CM code for branch retinal vein occlusion (BVO, 362.36). Patient age, gender, race, state of residence and Charlson Comorbidity Index (CCI) scores were collected. *Healthcare Common Procedure Coding System* (HSCPS) codes for bevacizumab (J3590, J9035, and J3490) and for ranibizumab (J2778) were used to identify the mode of treatment for each patient. Patients who met the following criteria were excluded from this study: (1) under 65 years of age; (2) residence outside of the 50 United States or the District of Columbia; (3) no Part-B coverage or with HMO coverage that was not processed by Centers for Medicare & Medicaid Services (CMS); (4) concomitant diagnosis of diabetic edema (ICD-9: 362.07) or central retinal vein occlusion (ICD-9: 362.35); and (5) received both or none of the above two treatments. Geographic variation was examined by comparing injection frequencies across the nine US census divisions using Chi-squared analysis.

Results: During 2010–2013, a majority of the 3944 BVO patients who met the inclusion criteria received bevacizumab compared to ranibizumab (76.7% vs 23.3%). Most patients were aged 75–79 (22.0%) or 80–84 (22.0%), female (61.5%), white (88.3%), and had a CCI score of 1–2 (39.8%). The frequencies of bevacizumab and ranibizumab injections for BVO varied significantly between the US census divisions ($p < 0.0001$). The highest frequencies of bevacizumab use were in the Mountain (90.6%) and Pacific (82.7%) divisions while the highest frequencies of ranibizumab use were in the West North Central (37.9%) and Mid Atlantic (32.7%) divisions.

Conclusions and Importance: A majority of Medicare beneficiaries with BVO received bevacizumab compared to ranibizumab from 2010 to 2013, with significant geographic variation in the use of the two anti-VEGF agents. Future research into factors driving geographic variation in the use of these agents may help direct cost-effective strategies for the management of BVO.

1. Introduction

Retinal vein occlusion (RVO) is the second most prevalent retinal vascular disease after diabetic retinopathy and can lead to ocular neovascularization and visually-threatening macular edema.[1,2] Prior studies have demonstrated the efficacy of anti-vascular endothelial growth factor (anti-VEGF) agents including bevacizumab (Avastin®, Genentech), ranibizumab (Lucentis®, Genentech), and aflibercept (Eylea®, Regeneron Pharmaceuticals Inc) in treating macular edema secondary to RVO and maximizing visual improvement in these patients.[3–8] However, across all disease states, the cost of intravitreal anti-VEGF agents alone accounted for more than $2.6 billion annually within the fee-for-service (FFS) Medicare population by 2014.[9]

Significant cost differences exist between agents; in 2015, per unit,

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bevacizumab cost on average $67.50 while ranibuzmab cost $387.25, and aflibercept cost $962.85 (5 units of ranibizumab and 2 units of aflibercept are typically administered in treating RVO).[9] In addition, considerable variation exists with respect to the use of intravitreal anti-VEGF agents for the management of RVO.[10–12] Previous studies have identified regional and provider factors associated with overall variation in anti-VEGF use.[10–15] However, the geographic variation of anti-VEGF use for the treatment of RVO has not been well described. The public release of FFS Medicare claims data by the Centers for Medicare and Medicaid Services (CMS) in 2014 has enabled greater transparency in drug and payment variation.[16] Herein, we used a 5% Medicare Denominator and Physician/Supplier Part B claims database obtained from the CMS to evaluate the frequency and geographic variation of bevacizumab and ranibizumab for branch retinal vein occlusion (BVO) among beneficiaries from 2010 to 2013. We omitted aflibercept from the study as its approval for use in BVO did not take effect until 2014.

2. Materials and methods

2.1. Data collection

We obtained a 5% random sample of Medicare beneficiaries from the Medicare Denominator and Physician/Supplier Part B claims files maintained by the CMS from 2010 to 2013. All Medicare beneficiaries with BVO were identified using the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis code for 362.36 and were extracted from the 5% Physician/Supplier Part B claims files.[15] The study was approved by the institutional review board of the University of California, Los Angeles.

All BVO patients were then merged with the 5% Denominator files, and their demographics, including age, gender, race, and state of residence, were extracted. The Charlson Comorbidity Index (CCI) scores were calculated based on the selected systemic diseases identified using ICD-9 diagnosis codes from the 5% Physician/Supplier Part B claims files. *Healthcare Common Procedure Coding System* (HCPCS) codes for bevacizumab (J3590, J9035, and J3490) and for ranibizumab (J2778) were used to identify the mode of treatment for each patient. The anti-VEGF agent aflibercept had not been approved by the US Food and Drug Administration (FDA) for use in BVO management until after the study period (October 2014) and was thus excluded from the present study.

Patients who met the following criteria were excluded from this study: (1) patients who were under 65 years of age; (2) patients who did not reside in the 50 United States or the District of Columbia; and (3) patients who did not have Part-B coverage or with HMO coverage that was not processed by CMS; (4) patients who had concomitant diagnosis of diabetic edema (ICD-9: 362.07) or central retinal vein occlusion (ICD-9: 362.35); and (5) patients who did not receive either of the above two treatments or if they received both types of treatment. All US regions were appropriately represented in the final sample.

2.2. Statistical analysis

Data analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC). Descriptive statistics were used to describe the characteristics for the study population. Geographic variation was examined by comparing injection frequencies across the nine US census divisions; Chi-square tests were used to calculate statistical significance of overall comparisons. Subgroup comparisons between two divisions were performed using Fisher exact test.

3. Results

A sample of 3944 patients was obtained (Table 1). Most patients were aged 75–79 (22.0%) or 80–84 (22.0%), female (61.5%), white (88.3%), and had a CCI score of 1–2 (39.8%).

Table 1
Baseline characteristics of patients receiving bevacizumab and ranibizumab injections for BVO from 2010 to 2013 (n = 3944).

Patient Characteristic	n (%)
Age (years)	
65–69	607 (15.4)
70–74	672 (17.1)
75–79	869 (22.0)
80–84	868 (22.0)
85–89	617 (15.6)
≥90	311 (7.9)
Sex	
Male	1520 (38.5)
Female	2424 (61.5)
Race	
White	3482 (88.3)
Black	262 (6.6)
Hispanic	59 (1.5)
Asian	71 (1.8)
Other or unknown	70 (1.8)
CCI score	
0	1100 (27.9)
1–2	1569 (39.8)
3–4	790 (20.0)
≥5	485 (12.3)
Anti-VEGF factor	
Bevacizumab	3025 (76.7)
Ranibizumab	919 (23.3)

BVO = branch retinal vein occlusion.
CCI = Charlson comorbidity index.
VEGF = vascular endothelial growth factor.

Table 2
Frequency of bevacizumab and ranibizumab injections within each United States Census Division[a] among patients with branch retinal vein occlusion (BVO) from 2010 to 2013 (n = 3944).

United States Census Division	Bevacizumab n (%)	Ranibizumab n (%)
New England	115 (78.8)	31 (21.2)
Mid Atlantic	380 (67.3)	185 (32.7)
East North Central	504 (79.0)	134 (21.0)
West North Central	190 (62.1)	116 (37.9)
South Atlantic	676 (76.0)	213 (24.0)
East South Central	205 (78.9)	55 (21.1)
West South Central	311 (81.0)	73 (19.0)
Mountain	213 (90.6)	22 (9.4)
Pacific	431 (82.7)	90 (17.3)

Data are no. (%).
[a] The census divisions are defined as follows: New England Division: Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont; Middle Atlantic Division: New Jersey, New York, Pennsylvania; East North Central Division: Illinois, Indiana, Michigan, Ohio, Wisconsin; West North Central Division: Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, South Dakota; South Atlantic Division: Delaware, District of Columbia, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, West Virginia; East South Central Division: Alabama, Kentucky, Mississippi, Tennessee; West South Central Division: Arkansas, Louisiana, Oklahoma, Texas; Mountain Division: Arizona, Colorado, Idaho, Montana, Nevada, New Mexico, Utah, Wyoming; Pacific Division: Alaska, California, Hawaii, Oregon, Washington.

From 2010 to 2013, the frequencies of bevacizumab and ranibizumab injections for BVO varied significantly between the US census divisions ($p < 0.0001$; Table 2). Among the sample population, a majority received bevacizumab compared to ranibizumab (76.7% vs 23.3%; see Table 3). The highest frequencies of bevacizumab use for BVO were in the Mountain (90.6%) and Pacific (82.7%) divisions while the highest frequencies of ranibizumab use were in the West North Central (37.9%) and Mid Atlantic (32.7%) divisions ($p < 0.0001$ for frequency distributions of Mountain v. West North Central, Mountain v.

Table 3
Yearly frequency of bevacizumab and ranibizumab injections among patients with branch retinal vein occlusion (BVO) from 2010 to 2013 (n = 3944).

Year	Bevacizumab n (%)	Ranibizumab n (%)
2010	713 (89.2)	86 (10.8)
2011	727 (80.3)	178 (19.7)
2012	784 (75.3)	257 (24.7)
2013	801 (66.8)	398 (33.2)

Data are no. (%).

Mid Atlantic, Pacific v. West North Central, Pacific v. Mid Atlantic).

4. Discussion and conclusions

This retrospective study using FFS Medicare claims data showed that bevacizumab accounts for a majority of anti-VEGF injections for the management of BVO in 2010–2013, although there is significant geographic variation in the use of bevacizumab and ranibizumab.

Bevacizumab was used more than three times as frequently as ranibizumab for BVO in our study period. In contrast, Erie and colleagues found a 1.7 ratio of bevacizumab to ranibizumab use for the management of various retinal diseases, including diabetic macular edema, RVO, and age-related macular degeneration (AMD) within a 2013 Medicare cohort. Our findings point to the importance of studying a specific condition to understand the nuances affecting overall variation of anti-VEGF use.

Physician factors may influence geographic variation of anti-VEGF use.[10,12,15] Studies have found positive correlations between pharmaceutical-related reimbursement and use of the higher-cost aflibercept and ranibizumab.[10,15] Additionally, states with higher numbers of Medicare beneficiaries relative to ophthalmologists administering anti-VEGF therapy tended to exhibit lower rates of intravitreal injections, and physicians in states with lower mean injection rates were more likely to use the lower-cost bevacizumab.[12]

Patient-level incentives may also affect agent selection. While bevacizumab represented the majority of injections for AMD within Medicare, the distribution between bevacizumab and ranibizumab was relatively equal from 2009 to 2011 within the Veterans Health Administration (VHA), an integrated healthcare system without financial prescribing incentives for physicians.[13] This may reflect higher Medicare copayments on ranibizumab, while service-connected disability and low-income exemptions reduce such financial pressures on VHA patients.[13] Most Medicare patients in our study period had low CCI scores (1–2), which may not be the case for other populations such as patients receiving care in the VHA[16]; further studies are needed to determine whether level of comorbidity among BVO patients affects utilization of anti-VEGF therapy. In certain practices, ranibizumab patients receive better coverage for drug costs (e.g. through charity pools, secondary insurance) and end up paying less out of pocket; such differences may explain the regional variation seen with respect to ranibizumab use. How these factors affect standardization and quality of BVO management merits further study.

The Medicare data files supply readily accessible nationwide patient information, thus providing a nationally representative cohort of geographically and racially diverse patients for study.[17] However, the use of this data has inherent limitations that have been described in detail elsewhere.[12,13] Additional limitations include lack of a benchmark upon which to define overutilization or underutilization of anti-FEGF therapy and limited generalizability to patients under 65 years of age or enrolled in other health plans. As ranibizumab was FDA approved for use in BVO in mid-2010, this may have limited its use in the initial year of our study period. It is possible that regional variations in use of ranibizumab may have been related to varying rates of reimbursement by state, particularly in the months following FDA approval. Our study does not include utilization data for aflibercept given that its approval occurred outside of the study window; FDA approval of aflibercept in 2014 may have further influenced utilization of the other two agents in subsequent years.

In summary, bevacizumab appears to be the agent of choice for most Medicare beneficiaries with BVO from 2010 to 2013, although significant geographic variation exists with respect to anti-VEGF use. It is important to note that during the period of this study, ranibizumab use in BVO tripled from 10.8% to 33.2% following its FDA approval in 2010. More recent cohort years need to be examined to better characterize current anti-VEGF utilization patterns in this disease, especially with the approval of Aflibercept for BVO in 2014.

Patient consent

The study was approved by the institutional review board of the University of California, Los Angeles.

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Conflicts of Interest

The following authors have no financial disclosures: AMW, CMW, PBG, FY, FL, ALC.

Authorship requirements

All authors attest that they meet the current ICMJE criteria for Authorship.

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