Published in final edited form as:

JAMA Ophthalmol. 2015 October 1; 133(10): 1159–1164. doi:10.1001/jamaophthalmol.2015.2556.

The association between compounding bevacizumab and post-injection endophthalmitis

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Abstract

Importance—Current draft guidelines set forth by the FDA for compounded or repackaged medications would greatly limit the availability and use of bevacizumab by ophthalmologists across the country. Little evidence outside of highly publicized case reports, exists for or against the need for additional regulation of compounding bevacizumab.

Objective—To determine if the distribution of bevacizumab through compounding pharmacies increases the risk of endophthalmitis compared to the distribution of single-use vials of ranibizumab from the manufacturer.

Design—This is a retrospective cohort study using medical claims data from a large, national U.S. insurer. Cohorts were created using intravitreal injections of bevacizumab and ranibizumab from 2005–2012.

Setting—Ambulatory care centers across the United States.

Participants—Any individual having an intravitreal injection of bevacizumab or ranibizumab with at least 6 months of data prior to the injection was eligible. Exclusion criteria consisted of any previous diagnosis of endophthalmitis, multiple injected drugs on the day of injection, or intraocular surgery within 15 days of the injection or between an injection and a diagnosis of endophthalmitis.

Main Outcome Measure—The main outcome was the proportion of intravitreal injections resulting in endophthalmitis.

Results—296,565 injections of bevacizumab were given to 51,116 patients and 87,245 injections of ranibizumab were given to 7,496 patients. A total of 71 cases of endophthalmitis (49 in the

bevacizumab cohort, 22 in the ranibizumab cohort) were seen for an endophthalmitis rate of 0.017% (CI: 0.012–0.021%; 1/6061 injections) for bevacizumab and 0.025% (CI: 0.015–0.036%; 1/3968) for ranibizumab. After controlling for age, race and gender, injection-related diagnosis, and year of injection, there was no significant association for developing endophthalmitis after a bevacizumab injection compared to ranibizumab (OR=0.66, 95% CI: 0.39–1.09, p=0.11).

Conclusions and Relevance—The results of this study suggest bevacizumab as currently used across the US does not increase the risk of endophthalmitis; therefore, additional regulations on the use of repackaged bevacizumab may be unnecessary.

Keywords

endophthalmitis; anti-VEGF; bevacizumab; ranibizumab; intravitreal injections; compounding; pharmacoepidemiology

Introduction

Multiple clinical trials have demonstrated that intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents are highly effective treatments for neovascular age-related macular degeneration (AMD) and macular edema due to diabetes (DME) or retinal vein occlusions (RVO).^{1–4} As such, injections of anti-VEGF agents have become standard care for these conditions. Despite the rise in the use of injections, endophthalmitis continues to be the most feared post-injection complication. Concern for this adverse event is central to the ongoing debate over the use of compounded or “repackaged” bevacizumab (Avastin®, Genentech, South San Francisco, CA.)

The lay press first brought this issue to the forefront of the public’s attention after widely reporting on several case series that were discovered within months of each other in 2011.^{5–8} Unfortunately, media sensationalism of this topic may have led to misplaced fear with headlines such as “Avastin injections are reported to cause blindness,”⁷ focusing on bevacizumab as the culprit and not the compounding process itself. The first (and to date only) peer-reviewed report to describe compounding-related endophthalmitis was published a few months after the lay press reports and described 12 cases of endophthalmitis in Florida, all linked to a single compounding pharmacy.⁹ This report appeared about a month after a “Letter to the Editor” of the New England Journal of Medicine describing the faulty practices witnessed at a compounding pharmacy in Tennessee thought to have led to another smaller contamination-related outbreak of endophthalmitis.¹⁰

Concerns over compounding were further increased after several deaths occurred due to a large outbreak of fungal meningitis linked to contaminated compounded solutions of steroids for intrathecal administration. In response to these concerns, Senate Bill 959 was introduced and would have allowed the FDA to ban all compounded medications, but the bill never made it through congressional approval.¹¹ In February 2015, after placing additional regulations on compounding pharmacies, the FDA also released a draft guidance specifically allowing the compounded use of bevacizumab, but included language regarding “beyond use dates” that limited use to within 5 days of repackaging.¹² This restrictive 5-day time frame does not allow for proper sterility testing (which typically takes 14 days) and

would negate the ability of most ophthalmologists to use bevacizumab. In response, the American Academy of Ophthalmology (AAO)¹³, the American Society of Retina Specialists (ASRS)¹⁴, and the Retina Society all issued calls to action delineating the specific concerns over the proposed new regulations and arguing for heavy lobbying against the draft guidance.

Despite this ongoing policy debate, the evidence for or against an increased risk of endophthalmitis due to repackaged bevacizumab is limited, and it is unclear if repackaging truly represents a public health hazard or if policy makers are being influenced by highly publicized isolated incidents. The purpose of this study is to compare the rates of endophthalmitis after intravitreal injections of bevacizumab and ranibizumab in a national cohort containing data from 2005 to 2012.

Methods

Dataset

The Clinformatics™ Data Mart Database (OptumInsight, Eden Prairie, MN) was used for this retrospective cohort study. This administrative medical claims database contains the de-identified billing claims of all covered individuals from a single large insurance company with beneficiaries in each of the 50 United States. All outpatient medical claims (office visits, procedures and medications given) and demographic data for each beneficiary during their enrollment are included. The subset of data available for this study included all patients in the database from January 1, 2005 to December 31, 2012. This study has been deemed exempt from review by the University of Pennsylvania's Institutional Review Board due to the de-identified nature of the database.

Study cohorts

All intravitreal injections (CPT code 67028) using bevacizumab and ranibizumab were identified within the dataset and divided into cohorts based on medicine injected. Each occurrence of an intravitreal injection was used as the index date and was considered a unique observation. Each index date was required to be preceded by at least 6 consecutive months in the insurance plan and 1 month following the injection. Any injection coded with a bilateral code (CPT 50) was considered to have had 2 injections. (See Table 1 for complete list of codes used during this study.)

At any point that an individual was given a diagnosis code for endophthalmitis, all future injections were removed from the analysis. Additionally, in an effort to isolate only cases of endophthalmitis related strictly to intravitreal injections, all index dates that occurred less than 15 days after an intraocular surgery or had an intraocular surgery occur between the index date and a diagnosis of endophthalmitis were also excluded. Lastly, any intravitreal injections involving more than one drug were excluded as well.

Outcome measures

The primary outcome measure for this study was the odds of developing endophthalmitis after an intravitreal injection of bevacizumab compared to ranibizumab. Cases of

endophthalmitis were defined by having a new endophthalmitis diagnosis code in conjunction with a code for a “tap and inject” procedure, a vitrectomy or an intravitreal injection of antibiotics. Cases had to occur from 1–14 days after index date. Cases that occurred on the same day as the index date were excluded due to an inability to distinguish if the intravitreal injection preceded the endophthalmitis defining procedure. A sensitivity analysis was also performed in which the definition of endophthalmitis was expanded. For this analysis, in addition to the definition of endophthalmitis previously stated, also included were cases that on the same day had a new diagnosis of endophthalmitis and an intravitreal injection (but were not required to have intravitreal antibiotics).

Odds ratios were calculated by logistic regression for both univariate and multivariate analyses. Covariates of interest were collected at the time of the index date and included basic demographic information; age, race and gender. Additionally the injection–associated diagnosis was categorized as either age-related macular degeneration (AMD), diabetic macular edema (DME), retinal vein occlusions (RVO) or other. Previous reports have suggested that the rate of endophthalmitis after intravitreal injection is decreasing with time.¹⁵ To account for any variation in the rates with time in the model, the year the injection was performed was included as a variable. STATA[®] 12 (College Station, Texas) software was used for all statistical analysis.

Results

A total of 383,810 intravitreal injections were given to 58,612 patients between 2005 and 2012 that met inclusion criteria for the study (Figure 1). Of these, 296,565 injections (51,116 patients) used bevacizumab and 87,245 injections (7,496 patients) used ranibizumab. (See Table 2 for cohort demographics) The bevacizumab cohort was younger and had a lower percentage of females ($p<0.001$ for both comparisons). With regard to race, the bevacizumab group consisted of a higher percentage of Black and Hispanic patients compared to the ranibizumab cohort ($p<0.001$). Although AMD was the most common injection-associated disease in both cohorts, the bevacizumab cohort consisted of more injections related to diabetes, retinal vein occlusions and “other” diagnoses ($p<0.001$).

A total of 71 cases of endophthalmitis (49 in the bevacizumab cohort, 22 in the ranibizumab) occurred in the observation period. The mean time to diagnosis was 4.75 (SD ± 3.53) days after injection. The overall rate of endophthalmitis was 0.018% (CI: 0.014–0.023%; 1 case/5411 injections) with individual rates of 0.017% (CI: 0.012–0.021%; 1/6061) for bevacizumab and 0.025% (CI: 0.015–0.036%; 1/3968) for ranibizumab. These rates correlated to a risk difference of 0.009% (95% CI: –0.020–0.0028%, $p=0.14$) with less endophthalmitis in the bevacizumab cohort. Univariate logistic regression analysis (Table 3) showed no association for intravitreal bevacizumab injections and endophthalmitis of 0.65 (95% CI: 0.40–1.08, $p=0.10$). After controlling for age, race, gender, year of injection and injection-associated diagnosis in the multivariate analysis, the odds ratio between bevacizumab and endophthalmitis was essentially unchanged at 0.66 (95% CI: 0.39–1.09, $p=0.11$) from the univariate analysis.. (Table 4) Sensitivity analysis with a less stringent definition of endophthalmitis increased the number of cases from 71 to 97 (69 bevacizumab and 28 ranibizumab), but did not appreciably alter the univariate (OR: 0.73, 95% CI: 0.47–

1.12, $p=0.15$) or the multivariate (OR: 0.70, 95% CI: 0.45–1.10, $p=0.13$) analysis results for the association between bevacizumab and endophthalmitis.

Discussion

To the best of the authors' knowledge, this is the largest single data source to evaluate the risk of endophthalmitis comparing bevacizumab to ranibizumab. This study analyzed over 296,000 injections of bevacizumab and over 87,000 injections of ranibizumab to find the rate of endophthalmitis after bevacizumab to be 0.017% (CI: 0.012–0.021%) and 0.025% (CI: 0.015–0.036%) for ranibizumab. Thus, bevacizumab as used across the United States was not associated with an increased risk of endophthalmitis compared to ranibizumab.

A central strength to this study is the manner in which the data were collected. As noted in many of the lay articles cited previously^{5–8}, numerous lawsuits have occurred due to contaminated injections, which may have biased against the public reporting of outbreaks. The data used in this study circumvents this issue as billing claims are part of the health record and are only offered to researchers after extensive statistical de-identification. This allows physicians to bill for endophthalmitis care without the concern of later public disclosure. A second advantage to this study was the use of a national cohort consisting of individuals from all 50 states. Given the sizable geographic distribution of the cohort, it is likely data from multiple compounding pharmacies are represented within this dataset. This is in comparison to large single center reports¹⁶ that are likely to have all of their bevacizumab come from a single pharmacy which only verifies the safety of that specific distribution site.

Lastly, it should be noted that the data used for this study was derived from 2005 to the end of 2012. This time frame is significant because no additional regulation of compounding pharmacies had been passed prior to 2013, and yet no difference in endophthalmitis rates was seen, suggesting additional regulation on bevacizumab may be unnecessary. This of course does not rule out the possibility of pharmacies evaluating their own practices and adjusting protocols as a reaction to the publicity of the outbreaks in late 2011, but again this would only further underscore that bevacizumab is currently distributed in a safe manner.

As noted in the call to action by the ASRS, the rate of endophthalmitis after intravitreal injections may actually be lower after bevacizumab than after ranibizumab due to the sterile protocols for loading bevacizumab syringes, compared to the typical office setting used to load ranibizumab.¹⁴ Although the OR reported in this study of 0.66 for endophthalmitis trended towards a protective effect for bevacizumab, this test did not reach significance ($p=0.11$). It is interesting to note; however, that the endophthalmitis rates after bevacizumab (0.018%) and ranibizumab (0.025%) found in this study were remarkably similar to those reported in another very large single cohort of injections by Flynn and colleagues for both bevacizumab and ranibizumab (0.013%, 0.020%, respectively) (Written communication, ARVO 2015-abstract #4193-C0076"). These results were also consistent with several smaller previous studies.^{16–18} The failure to find a significantly lower OR in this study may simply be due to a lack of statistical power and a larger study (either a single cohort or meta-analysis of available data) may in fact find a protective effect. This possibility needs to be

given strong consideration because if true, any FDA regulations aimed at reducing endophthalmitis by limiting repackaged bevacizumab, may actually have the unintended consequence of increasing endophthalmitis rates by shifting usage to less safe office loaded syringes.

Although the medical claims data used for this analysis provides several strengths as noted above, there are limitations that need to be addressed. First, due to the de-identified nature of claims data, we are unable to verify each case of endophthalmitis by reviewing a specific patient's chart. To reduce this potential limitation, separate analyses were run using both a more strict definition as well as a more relaxed definition of endophthalmitis in a sensitivity analysis. No difference was seen between the analyses. An additional limitation was the inability to ascertain the culture positive/negative status of each endophthalmitis case. Although misclassification of endophthalmitis is a possibility in this study, there is no reason to believe there would be a bias favoring less endophthalmitis in bevacizumab, particularly given previous reports^{19,20} showing higher incidence rates of sterile inflammation after bevacizumab injections compared to ranibizumab. Next, due to the de-identified nature of the data, there is no way to identify which compounding pharmacies were used to supply the bevacizumab in this study. Also, the data used in this study comes from a single medical claims database. It is unclear if a similar study performed in a different medical claims database (e.g. Medicare) would yield similar or different results.

Lastly, there is no specific billing code for a single use vial of bevacizumab to contrast to bevacizumab that was derived from a compounded batch. This allows for the possibility that non-compounded bevacizumab was used in this study; however, given the reimbursement rates for bevacizumab injections (~\$50–\$80) and relatively expensive cost of single use bevacizumab (~\$500), each physician choosing this option would be losing money on every injection given, making the likelihood of this occurring in a significant portion of the 296,000 injections studied very low.

This study examines a national cohort likely representing numerous compounding pharmacies across the country and found that the manner in which bevacizumab was used from 2005 to 2011 did not alter the risk of endophthalmitis compared to ranibizumab. Although contamination of compounded medications are an issue that needs constant vigilance, this study supports the idea that tight adherence to current compounding protocols and practice standards can assure the safe use of bevacizumab in ophthalmic practice without additional regulation.

ACKNOWLEDGMENT

Financial Support: National Institutes of Health K12 Award (Dr. Brian VanderBeek, K12-EY015398). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. Additional funding was provided by Research to Prevent Blindness and the Paul and Evanina Mackall Foundation. Funding from each of the above sources was received in the form of block research grants to the Scheie Eye Institute. None of the organizations had any role in the design or conduction of the study. This specifically includes the collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication. Authorship contributions BVB: study design, data analysis and interpretation, manuscript preparation and review; SGB: data interpretation, manuscript preparation and review; LM: data collection, statistical analysis, manuscript review. BVB had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis."

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Figure 1.

Number of injections that met inclusion and exclusion criteria. Insufficient time in the plan is defined as less than 6 months of data prior to the injection index date.

Table 1

Codes used within this study

Diagnosis	ICD9 CODES
Endophthalmitis	360.0x, 360.1x
Diabetes	250.xx, 362.0x, 362.82
Age-related Macular Degeneration	362.50, 362.51, 361.52
Retinal Vein Occlusion	362.3x
Cystoid Macular Edema	362.53, 362.83
Other Neovascularization	362.16, 365.83, 365.89
PROCEDURES	CPT CODES
Intravitreal injection	67028
Vitreous tap	67015
Vitreous tap and injection	67025
Pars Plana Vitrectomy	67036
Intraocular Surgery	650xx-653xx, 657xx-660xx, 671xx, 67250, 67255, 67299
DRUGS	DRUG CODES
Bevacizumab	J3590, J9035, J3490, C9257, C9399, Q2024
Ranibizumab	J2778, C9233

Table 2

Baseline characteristics of bevacizumab and ranibizumab cohorts

	Bevacizumab	Ranibizumab	P value
Total injections	296,565	87,245	
Avg age in years ($\pm$ SD)	74.7 (10.0)	76.6 (7.9)	<0.001
Female	58.9%	60.6%	<0.001
Race (%)			<0.001
White	79.4%	80.0%	
Black	6.7%	5.3%	
Hispanic	4.6%	3.7%	
Asian	1.5%	1.1%	
Other/Unknown	7.8%	9.9%	
Diagnosis (%)			<0.001
AMD	227,286 (76.6)	79,010 (90.6)	
Diabetes	34,222 (11.5)	2,204 (2.5)	
Retinal Vein Occlusion	25,493 (8.6)	5,244 (6.0)	
Other	7,848 (2.7)	331 (0.4)	
Multiple	1,716 (0.6)	456 (0.5)	

Table 3

Unadjusted odds ratios for developing endophthalmitis

	Unadjusted Odds Ratio	95% CI	P Value
Age, each additional year	0.99	0.97–1.01	0.48
Gender			
Male	1.00		
Female	0.99	0.62–1.56	0.97
Year of injection	0.91	0.79–1.04	0.16
Race			
White	1.00		
Black	1.23	0.53–2.84	0.63
Hispanic	-	-	-
Asian	-	-	-
Unknown	0.62	0.23–1.73	0.37
Diagnosis			
Diabetes	1.00		
AMD	1.19	0.51–2.75	0.69
Retinal Vein Occlusion	0.99	0.30–3.24	0.98
Other	-	-	-
Multiple	-	-	-
Bevacizumab	0.65	0.40–1.08	0.10

“-“ Inadequate data for calculation

Table 4

Adjusted odds ratios for developing endophthalmitis

	Adjusted Odds Ratio	95% CI	P Value
Age	0.98	0.96–1.01	0.22
Gender			
Male	1.00		
Female	0.99	0.62–1.60	0.97
Year of injection	0.91	0.79–1.05	0.20
Race			
White	1.00		
Black	1.23	0.53–2.84	0.63
Hispanic	-	-	-
Asian	-	-	-
Unknown	0.62	0.23–1.73	0.37
Diagnosis			
Diabetes	1.00		
AMD	1.16	0.46–3.35	0.75
Retinal Vein Occlusion	1.00	0.30–3.24	0.99
Other	-	-	-
Multiple	-	-	-
Bevacizumab	0.66	0.39–1.09	0.11

“-“ Inadequate data for calculation