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Predictive factors for patients receiving intravitreal anti-VEGF for the treatment of diabetic macular edema

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Abstract

Purpose—To determine if anemia and other demographic or laboratory “risk factors” impact anti-VEGF treatment in DME patients.

Methods—This is a retrospective, time-varying cohort study using a medical claims database to identify new DME patients who had received at least one intravitreal injection of anti-VEGF. Exclusion occurred for having <2 years in the plan prior to DME diagnosis, any history of proliferative retinopathy or any treatment that is used for DME. Covariates of interest were demographic characteristics, laboratory values and clinical factors such as previous anti-VEGF used, number of involved eyes, year of treatment, and time since last injection. Those variables that changed with time were assessed and updated at each visit. The main outcome measure was the odds of receiving treatment at any visit.

Results—189 new DME patients with follow up were analyzed, covering 729 visits with 543(74.5%) receiving treatment. Univariate analysis showed that male gender(OR:0.54,95%CI: 0.32–0.91,p=0.03), every week since last injection(OR:0.94,95%CI:0.91–0.97,p=0.001), and having two eyes affected(OR:2.09,95%CI:1.10–3.97,p=0.02) were associated with getting an injection. After multivariate analysis, only time since previous injection with every week that passed reduced the odds on having an injection at the next visit(OR:0.95,95%CI:0.92–0.97,p<0.001). Anemia was not associated with receiving an injection(OR:1.05,95%CI:0.61–1.80,p=0.86).

Conclusions—This study used time-varying methodology to better identify which patients will likely need an injection at any one visit. While anemia was not found to impact injections, our

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results can aid future endeavors that may incorporate clinical visit information in developing a full prediction model to help make DME care more efficient.

Keywords

Intravitreal injections; DME; risk factors

INTRODUCTION

The success of intravitreal anti-vascular endothelial growth factor (VEGF) therapy for diabetic macular edema (DME) comes with a high burden of care including the costs of frequent patient visits, repeated treatments, and increasing stress on the overall healthcare system and patient alike [1–3]. As recently as 2015, the three common intravitreal anti-VEGF agents used to treat DME have each individually accounted for over \$1 billion in total United States (US) Medicare Part B expenditure [4]. With a reported prevalence of DME among diabetic patients in the US from 3%–10%, the ability to identify patients that may require more or less treatment is a critical issue [5–7]. In addition, as health care delivery pushes towards population health using “shared risk” models that link reimbursement with outcomes, both efficiency and effectiveness is expected.

Vitreous VEGF levels have been found to be highly correlated to the presence of DME, demonstrating a distinct gradient within the vitreous cavity, with pre-macular levels being the highest in DME patients [8–9]. Despite the correlation between ischemia and VEGF levels being well established, it is less clear if other mediators of oxygen delivery, namely, anemia, can influence VEGF levels and subsequently, the need for DME treatment [10–11]. Surprisingly, despite being reported as an independent risk factor for progression of diabetic retinopathy by the Early Treatment Diabetic Retinopathy Study group, anemia has rarely been evaluated as a factor in other progression studies and has yet to be assessed with regards to therapeutic impact [12–13].

Prior studies have identified multiple other clinical factors, such as hemoglobin A1c, hypertension, serum creatinine, and estimated glomerular filtration rate (eGFR), as being closely associated with DME [5,14–15]. Naturally, these associations have prompted further investigation to determine if these factors also affect treatment response of DME with most finding no association [16]. Poor glycemic control, however, has been found to be associated with a worse response to bevacizumab [17–18]. Despite clear pathophysiologic rationale, no single study has evaluated kidney function, anemia, and glycemic control and their potential impact on the need for DME treatment.

Therefore, numerous systemic clinical factors may not only help to predict a response to treatment but may also aid in predicting the need for a future treatment. With such information, it may be possible to develop patient-specific treatment plans and provide more streamlined, lower resource-utilizing care. Prior to the creation of any prediction model, however, meaningful risk factors need to be established. The primary purpose of this study is to evaluate the potential association of anemia on DME patients receiving an anti-VEGF treatment. Of course, to properly accomplish this goal, other common demographic, clinical, and metabolic characteristics also need to be evaluated. A secondary purpose of this study is

to assess these other factors to best identify which patients with DME are at the greatest “risk” to receive anti-VEGF therapy.

METHODS

Dataset and Subjects

Data were abstracted from the de-identified Clinformatics™ Data Mart Database (OptumInsight, Eden Prairie, MN), which contains the medical claims of all patients from a large managed care network from across the United States. Included within the database are all outpatient medical claims (office visits, procedures, and medications given) as well as demographic data and some laboratory values for all patients enrolled in the insurance plan. The subset of data available for this study included all patients from January 1, 2007 to December 31, 2016 in the database. Due to the de-identified nature of the database, the University of Pennsylvania’s Institutional Review Board deemed this study exempt from review.

All patients who were diagnosed with DME and initially treated with an anti-VEGF agent were included within this study. The use of diagnosis and treatment codes for diabetic macular edema has been validated previously [19–20]. DME was specifically defined as a diagnosis code for edema in addition to a current or previous diagnosis of diabetes. The index date for each person was considered the first date the DME was treated. For inclusion into the study, individuals had to be over 18 years old, have at least 24 consecutive months in the plan prior to the index date, and have had a hemoglobin level drawn within 12 months of the index date.

Individuals were excluded if at any time prior to the index date, they had a diagnosis for a disease that may be confused for DME including proliferative retinopathies, sickle cell disease, vein occlusions, pathologic myopia, retinoschisis, age-related macular degeneration, cystoid macular edema, all uveitides, and glaucoma. Since cystoid macular edema is a common complication of intraocular surgery, all patients with a code for an intraocular surgery within 90 days of index were also excluded. Additionally, exclusion occurred for all patients who had a history of any type of treatment that is used in the treatment of diabetic retinopathy. Lastly, patients that were part of categories of variables with less than 10 total patients or patients with erroneous lab values (i.e hemoglobin A1c of 191%) were also excluded. Table 1 contains all diagnosis, procedure, and drug codes used in the study.

Risk Factors

Numerous risk factors were assessed for their potential impact on the association of receiving treatment at any ophthalmic visit. The demographic variables were assessed at the index date and included age, race, gender, region of the country, yearly income, and education level. Similarly, clinical variables were also assessed at the index date and included history of hypertension and the Diabetes Complications Severity Index (DCSI) to better control for severity of underlying diabetic disease state [21]. This score was created from six categories of diabetic complications using outpatient ICD9/ICD10 codes and applied to each patient. This metric has been validated and found to predict clinically

relevant outcomes more accurately than traditional markers of diabetic severity such as glycosylated hemoglobin and duration of disease [21]. By DCSI definition, all patients included in this study had a score of at least one due to their non-proliferative diabetic retinopathy status.

Other variables known to fluctuate were assessed at each the index date and again at every ophthalmic follow up visit. This included hemoglobin A1c, serum creatinine, eGFR, and hemoglobin. The eGFR was calculated via the Modification of Diet in Renal Disease manner [22]. Hemoglobin was used to evaluate anemia in two forms: 1) as an ordinal variable with severity based on the World Health Organization guidelines for men and women and 2) as a binary variable [23]. In addition, time-varying clinical factors were also assessed including number of eyes affected, time since last treatment (in weeks), anti-VEGF drug used at previous injection, and, in order to assess treatment patterns that may have varied over time, the calendar year of treatment.

Outcome Measures

The primary outcome for the study was the odds of receiving an anti-VEGF injection at any particular visit. To do this, every visit to an ophthalmologist after the index date was assessed, and the patient was determined to have either received or not received an injection at that visit. Logistic regression using general estimating equations was used to find the odds ratio for each of the above listed variables in a time-varying manner while accounting for the potential correlation of multiple longitudinal assessments made within the same person. Patients were followed until the end of eligibility or the end of the observation period occurred. Patients were censored if they progressed to proliferative diabetic retinopathy or had any disease or treatment of exclusion noted earlier. Due to the numerous risk factors evaluated, only factors that had a p-value less than 0.2 were included in the multivariate analysis. P-values less than 0.05 were considered significant. Statistical analysis was performed using SAS (version 9.4; SAS Institute Inc., Cary, NC).

RESULTS

After inclusion and exclusion criteria, 246 patients met initial DME treatment criteria, but only 189 DME patients had a follow up visit prior to the end of the observation period and were included for analysis (Figure 1). These 189 subjects accounted for 729 visits after their initial injection at the index date, of which 74% (543) included a treatment. On average, each patient who followed up had 3.9 visits. The average age was 64.0 years (± 11.3), 60.8% (115) were men, and 65.6% (124) were white. Among metabolic factors, mean hemoglobin A1c was 8.6% (± 2.2), mean serum creatinine was 1.4 mg/dL (± 1.1), 22.2% (42) had normal eGFR, and 63.0% (119) were not anemic. See Table 2 for all baseline characteristics.

Univariate analysis showed that male gender (OR:0.54, 95%CI:0.32–0.91, $p=0.03$) and each additional week of time since last injection (OR:0.94, 95%CI:0.91–0.97, $p=0.001$) were protective for needing an injection at the subsequent visit. The only factors associated with higher odds of treatment was having a second eye affected (OR:2.09, 95%CI:1.10–3.97, $p=0.02$). Other factors that had a p-value less than 0.2 that were assessed in the final multivariate model included region of the country, age, and calendar year; anemia was also

included given its role as the primary outcome measure. See Table 3 for all univariate results.

After multivariate analysis, only time since last injection (OR:0.95, 95%CI:0.92–0.97, $p<0.001$) was still associated with receiving an injection. Anemia assessed as either a binary variable (Yes/No, $p=0.87$) or as an ordinal variable (normal, mild, moderate/severe, $p=0.69$) was not associated with receiving an injection. Age ($p=0.39$), year of treatment ($p=0.07$), male gender ($p=0.07$), region of the country ($p=0.22$), and number of eyes affected ($p=0.32$) were also not associated after adjusting for other variables. See Table 4 for full multivariate results.

DISCUSSION

The benefits of optimizing the number of visits and injections in the treatment of DME are significant for both patients and providers. Our initial hypothesis tested if anemia impacted treatment. In order to best assess this, numerous other factors had to be tested and considered simultaneously. Complicating this issue is that many of the factors that could be associated with receiving an injection are not static and change with time. This is the first study to use a time-varying statistical approach to assess numerous factors that may be associated with receiving an intravitreal injection at any one visit. Although the literature suggests real world providers administer fewer injections than those described in the larger DME trials, the possibility of targeting the “highest risk” patients may have long term effects on decreasing treatment burden while simultaneously improving visual outcomes [24–25].

Previous reports have suggested that diabetic retinopathy patients have more rigid erythrocytes than non-diabetic patients, resulting in reduced blood flow and increased aggregation at the capillary level [26–28]. Given this, it is then reasonable to wonder if patients in anemic states have further impairment of oxygen delivery that could exacerbate this issue, making more frequent injections for the treatment of DME necessary. As the primary outcome assessed in this study, we found no evidence that anemia impacts the need for anti-VEGF treatments.

We did find that each passing week since the previous injection decreases the odds of needing an injection at the next visit. This is consistent with the Diabetic Retinopathy Clinical Research Network (DRCRnet) trials that allowed for extension between visits once patients stabilized and is also intuitive. If a patient does not need an injection at 16 weeks, it is reasonable to assume a lower likelihood of needing an injection at 20 weeks. In our final model, male gender narrowly missed a significant association with having reduced odds of having an injection (OR:0.63, 95% CI: 0.39–1.00, $p=0.07$). In the major DRCRnet DME trials, men were required to have a larger central retinal subfield thickness for inclusion and treatment [3,29–30]. One reasonable explanation for our finding could be that practitioners outside of the trials are applying these stricter measures to men within their daily practice.

Similarly, the calendar year in which the injection was given overall was not significantly associated with receiving an injection ($p=0.10$), however, the odds ratio for the year 2016 was 3.51, with a significant 95% confidence interval (1.18–10.45). Despite the overall lack

of significance, this factor may be important to assess in future studies as new therapies take time to slowly diffuse into the greater practicing community only as more and more studies re-enforce that anti-VEGF therapy should be the gold standard for DME. These findings may also aid in better interpreting previously reported practice patterns and lower rates of anti-VEGF usage, which did not assess past 2014, unlike this study.

One strength of this study was the time varying approach used to assess these variables. Frequently in ophthalmology, risk factor studies assess only a baseline level of a variable at the initiation of a clinical trial or observation period and then carry it forward over many years. This contradicts the underlying nature of many of these variables as they often change with time and should be assessed as such, prior to being fully ruled out as predictive or not.

In contrast, several limitations also need to be considered when evaluating the results of this study. First, this study used a large de-identified insurance claims database that prevents the ability to review individual charts and verify diagnoses and treatments. Additionally, we were unable to include specific clinical data that may be relevant for future studies like visual acuity and central retinal thickness. This is particularly important for new patients who had 20/50 vision or worse, a group in which the DRCRnet Protocol T demonstrated aflibercept to have a higher efficacy [31]. Lastly, each decision to treat was at the discretion of the individual physicians. We cannot be certain that different practice patterns between physicians (i.e. one patient that one physician would treat would not have been treated had they been seen by another different physician) did not influence the results.

While it is disappointing further insights were not gained about specific systemic and metabolic factors within this study as they relate to requiring retreatment, it is still reassuring that this information can safely be excluded from future analyses. This is particularly important since future work in this area will likely require real world data, not data from a clinical trial where visits and treatments are often mandated by protocols. Real world data allows for pragmatic “mini-trials” to occur and information about these “mini-trials” can be exploited to better inform the care of DME patients. Seen within this light, this study still carries importance since most real-world data sets are either systemically focused (therefore lacking specific eye level data, similar to this dataset) or are eye focused (like the IRIS registry, which is rich with eye level data, but deficient in systemic and laboratory data). Knowing which information to ignore can often be as helpful as knowing which requires attention.

In conclusion, we found that a longer duration since last injection was associated with a reduced odds of receiving a treatment. Otherwise, no association was found for the majority of covariates in this study, including all of the metabolic biomarkers. Although few variables were found to be associated, this study helps to resolve their need for future use in upcoming predictive studies. Additional factors not analyzed in this study, especially those that are dynamic from one visit to the next (visual acuity, central retinal thickness), are of particular interest to include in future investigations that should use similar time-varying methodology. One can imagine a day when clinicians are able to adjust a patient’s schedule on a visit-to-visit basis using a simple algorithm that predicts future need of injections, which would

ensure more efficient health care delivery. Great potential still exists for using this statistical model in the future in order to provide more targeted treatment of DME.

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Fig 1.
Flowchart of patients with anti-VEGF injection that met inclusion and exclusion criteria.

Table 1.

Codes used within this study

DIAGNOSIS	ICD9 CODES	ICD10 CODES
Diabetes mellitus	250.xx	E08.xx-E13.xx
Nonproliferative diabetic retinopathy	362.01, 362.03, 362.04,362.06	
Diabetic macular edema	362.07, 362.53, 362.82,362.83	E08-E13 with.31x-.34x(exclude .3x9)
Proliferative diabetic retinopathy	362.02, 362.15, 362.16,362.29, 364.42,365.63,365.89	E08-E13 with.35x
Vitreous hemorrhage	379.23	H43.1x
Tractional retinal detachment	361.81, 361.9	H33.4x
Sickle cell disease	282.6x	D57.x
Other retinopathy	362.2x	H35.x
Retinal vascular occlusion	362.3x	H34.8x, H34.0x, H34.1x, H34.2x
Cystoid macular edema		H35.35x H35.81, H35.89
Serous retinal detachment	362.4x	H33.2x
Age related macular degeneration/ choroidal neovascularization	362.5x, 362.16	H35.32x, H35.73, H35.05x
Glaucoma	365.xx	H40.xx
Hypertension	401.xx-405.xx	I10.xx-I16.xx
Hematologic disorder/malignancy	200.xx-202.xx, 203.00-203.02, 204.xx, 238.71- 238.79, 283.0x, 285.22,V58.11	C81.x-C86.x, C88.x, C90.x-C-96.x,D46.x, D59.x, D63.0x, Z51.1
Nephropathy	250.4x, 580.xx-583.xx,585.xx, 586.xx, 593.9x	E08-E13 with .2x, N00.x-N08.x,N11.x, N15.x-N19.x
Neuropathy	250.6x, 337.0x-337.1x,354.0-355.9, 356.9x,357.2x, 358.1x, 458.xx,536.3x, 564.5x, 596.54,713.5x, 951.0x, 951.1x,951.3x	E08-E13 with .4x, G50.x-G59.x,G54.5x, G60xx-G65.x, G90.x, I95.1,K31.84, M14.60, N31.x, S04.x
Cerebrovascular disease	431.xx,433.xx-436.xx	G45.x, I60.x-I69.x
Cardiovascular disease	410.xx-414.xx, 427.1x,427.3x-427.5x, 428.xx, 429.2x, 440.xx, 441.xx	I20.x-I25.x, I46.x, I47.x, I49.x, I50.x,I70.x, I71.x (exclude I70.2x, I70.31x)
Peripheral vascular disease	0.4x, 250.7x, 442.3x,443.81, 443.9x, 444.22,707.1, 785.4x, 892.1x	E08-E13 with .5x and .6x, I72.x, I72.21x,I70.31x, I73.x, I74.x, S91.x
Metabolic disorders	250.1, 250.2, 250.3	E08-E13 with.0x and .1x
PROCEDURES	CPT CODES	
Intravitreal injection	67028	
Prior intraocular surgery	650xx-653xx, 657xx-659xx, 66xxxx, 670xx-672xx	
DRUGS	DRUG CODES	
Bevacizumab	J3590, J9035, J3490, C9257, C9399, Q2024	
Ranibizumab	J2778, C9233	
Aflibercept	J0178, C9291	
Triamcinolone	J3300-J3303	
Dexamethasone	J1100, J7312	

Table 2.

Baseline characteristics of patients analyzed.

	Total (N=189)
Age mean(SD)	64.0 years(11.3)
Gender	
Male	115(60.8%)
Female	74 (39.2%)
Race	
White	124(65.6%)
Black	28(14.8%)
Asian	6(3.2%)
Hispanic	31(16.4%)
Educationlevel	
High School Diploma or less	73(38.6%)
< Bachelor Degree	94(49.7%)
Bachelor Degree or >	22(11.6%)
Household income	
<\$40K	49(25.9%)
\$40K-\$49K	20(10.6%)
\$50K-\$59K	14(7.4%)
\$60K-\$74K	18(9.5%)
\$75K-\$99K	21(11.1%)
\$100K+	45(23.8%)
Unknown	22 (11.6%)
Geographic distribution	
Upper Midwest	24(12.7%)
Southern Midwest	49(25.9%)
Northeast	20(10.6%)
Mountain	23(12.2%)
Pacific	13(6.9%)
South Atlantic	60(31.7%)
Hypertension	175(92.6%)
Blood disorder/cancer	2(1.1%)
DCSI	
[1,2]	72(38.1%)
[3,4]	49(25.9%)
[5,11]	68(36.0%)
Hemoglobin A1c mean (SD)	8.6%(2.2)
Serum Creatinine mean (SD)	1.4 mg/dl(1.1)
eGFR	
Unknown	1(0.5%)

	Total (N=189)
Normal	42(22.2%)
Mild	62(32.8%)
Moderate/Severe	27(14.3%)
Severe	16(8.5%)
End stage disease/dialysis	5(2.6%)
Number of eyes effected	
1	180(95.2%)
2	9(4.8%)
Calendar year	
2007–11	17(9.0%)
2012	13(6.9%)
2013	41(21.7%)
2014	37(19.6%)
2015	34(18.0%)
2016	47(24.9%)
Anemia	
Normal	119(63.0%)
Mild	44(23.3%)
Moderate/severe	26(13.8%)

Table 3.

Univariate analysis of the association between covariates and the probability of receiving an injection.

Variable	Cases (n, %)	OR (95% CI)	P-value
Anemia			0.60
Normal	326 (74%)	REF	
Mild	140 (78%)	1.23 (0.68, 2.26)	
Moderate/Severe	71 (70%)	0.81 (0.38, 1.71)	
Anemia			0.86
No	326 (74%)	REF	
Yes	211 (75%)	1.05 (0.61, 1.80)	
Age		1.03 (1.00, 1.06)	0.10
Gender			0.03
Female	232 (81%)	REF	
Male	305 (70%)	0.54 (0.32, 0.91)	
Race			0.36
White	371 (73%)	REF	
Black	75 (82%)	1.64 (0.78, 3.45)	
Hispanic	68 (72%)	0.97 (0.48, 1.97)	
Asian	23 (82%)	1.71 (1.06, 2.77)	
Education			0.77
HS Diploma or Less	186 (74%)	REF	
< Bachelor Degree	290 (73%)	0.97 (0.55, 1.70)	
Bachelor Degree or >	61 (79%)	1.33 (0.55, 3.25)	
Household income (US \$)			0.51
<\$40K	140 (81%)	REF	
\$40K - \$49K	54 (78%)	0.82 (0.36, 1.91)	
\$50K - \$59K	29 (78%)	0.83 (0.39, 1.74)	
\$60K - \$74K	42 (71%)	0.56 (0.21, 1.50)	
\$75K - \$99K	51 (70%)	0.53 (0.20, 1.40)	
\$100K+	153 (73%)	0.61 (0.27, 1.37)	
Unknown	68 (66%)	0.44 (0.22, 0.91)	
Geographic distribution			0.18
Upper Midwest	70 (60%)	REF	
Southern Midwest	148 (81%)	2.84 (1.15, 6.98)	
Northeast	65 (71%)	1.68 (0.63, 4.50)	
Mountain	44 (73%)	1.85 (0.58, 5.84)	
Pacific	73 (87%)	4.46 (1.63, 12.17)	
South Atlantic	137 (73%)	1.80 (0.75, 4.35)	
History of Hypertension			0.57
No	30 (79%)	REF	
Yes	507 (74%)	0.76 (0.30, 1.95)	
Previous Drug *			0.70

Variable	Cases (n, %)	OR (95% CI)	P-value
Bevacizumab	332 (75%)	REF	
Aflibercept	89 (72%)	0.89 (0.42, 1.87)	
Ranibizumab	105 (77%)	1.12 (0.61, 2.05)	
Unknown	11 (61%)	0.53 (0.25, 1.14)	
Every week since last injection		0.94 (0.91, 0.97)	0.001
Number of eyes effected			0.02
1	434 (72%)	REF	
2	103 (84%)	2.09 (1.10, 3.97)	
Calendar year			0.10
2007–2011	14 (56%)	REF	
2012	36 (80%)	3.14 (1.09, 9.09)	
2013	87 (71%)	1.95 (0.75, 5.12)	
2014	98 (70%)	1.79 (0.67, 4.79)	
2015	110 (71%)	1.96 (0.72, 5.39)	
2016	192 (81%)	3.43 (1.37, 8.59)	
DCSI			0.94
[1, 2]	177 (75%)	REF	
[3, 4]	141 (73%)	0.92 (0.54, 1.56)	
[5, 11]	219 (75%)	1.00 (0.53, 1.89)	
Hemoglobin A1c^{**}		1.06 (0.95, 1.18)	0.33
Serum Creatinine		0.98 (0.73, 1.33)	0.91
eGFR^{**}			0.32
Normal	17 (61%)	REF	
Mild	50 (75%)	0.94 (0.58, 1.53)	
Moderate	108 (85%)	1.25 (0.61, 2.58)	
Moderate/Severe	102 (76%)	2.24 (1.10, 4.54)	
Severe	168 (71%)	1.16 (0.49, 2.75)	
End stage dialysis	89 (72%)	0.61 (0.15, 2.50)	

* 6 observations with Aflibercept/Ranibizumab or Aflibercept/Bevacizumab were not included in the analysis

** data missing for some observations

Table 4.

Multivariate analysis of the association between covariates and the probability of receiving an injection *

Variable	OR (95% CI)	P-value
Anemia (Normal Ref)		0.69
Mild	1.16 (0.71, 1.90)	
Moderate/Severe	0.86 (0.48, 1.55)	
Anemia (Binary)	1.04 (0.68, 1.58)	0.87
Age	1.01 (0.99, 1.04)	0.39
Gender (Female Ref)	0.63 (0.39, 1.01)	0.07
Geo. Dist (Up Midwest Ref)		0.22
Southern Midwest	2.06 (1.06, 4.01)	
Northeast	1.12 (0.51, 2.48)	
Mountain	1.50 (0.59, 3.82)	
Pacific	3.15 (1.22, 8.14)	
South Atlantic	1.34 (0.68, 2.64)	
Every week since last injection	0.95 (0.92, 0.97)	<0.001
# eyes effected (1 Ref)	1.37 (0.72, 2.60)	0.32
Calendar year (2007–11 Ref)		0.07
2012	2.79 (0.83, 9.45)	
2013	1.88 (0.62, 5.69)	
2014	1.85 (0.60, 5.72)	
2015	2.10 (0.66, 6.73)	
2016	3.53 (1.18, 10.54)	

* Anemia is the primary predictor and only covariates with significance level <0.2 in the univariate analysis were included in the multivariate analysis. Anemia was tested separately and reported in two ways as an ordinal variable and as a binary (Yes/No) variable