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Treatment Patterns for Myopic Choroidal Neovascularization in the United States

Analysis of the IRIS Registry

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Purpose: To characterize treatment patterns and outcomes in eyes with treatment-naïve myopic choroidal neovascularization (mCNV) in the United States.

Design: Retrospective cohort study.

Participants: Individuals aged 18 years and older seen in clinics participating in the American Academy of Ophthalmology's IRIS (Intelligent Research in Sight) Registry.

Methods: We analyzed data from the IRIS Registry, from January 1, 2012 to December 31, 2014, to identify cases of treatment-naïve mCNV, which was defined as the presence of myopic refractive error worse than −6.0 diopters with the presence of subretinal/choroidal neovascularization as indicated by International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis of "362.16: Retinal Neovascularization NOS."

Main Outcome Measures: Type of initial treatment for mCNV was categorized as the administration of 1 of the following within the first 365 days after the diagnosis date: (1) observation (i.e., no treatment); (2) intravitreal anti-VEGF injection; (3) verteporfin photodynamic therapy (vPDT); or (4) laser photocoagulation. We assessed the difference between logarithm of the minimal angle of resolution (logMAR) visual acuity (VA) on the diagnosis date (baseline) and 1 year after the diagnosis date. Anti-VEGF injection frequency per treated eye over a 1-year period was also estimated.

Results: We identified 185 patients with treatment-naïve mCNV in 1 or both eyes. Treatment within 1 year of diagnosis was recorded for 73.0% (135/185); the remainder was classified as "observation." Nearly all treatment (134/135; 99.3%) consisted of anti-VEGF injections; 0.7% (1/135) received vPDT. Those treated with anti-VEGF injections showed significant improvement in VA at 1 year (mean logMAR VA improvement of 0.17 units, 95% confidence interval [CI], 0.12−0.20, $P < 0.01$), whereas those who were not treated showed a significant decline in VA at 1 year (mean logMAR VA decline: 0.03 units, 95% CI, 0.008−0.05, $P < 0.01$). The mean number of anti-VEGF injections for an eye with mCNV during the first year after diagnosis was 2.8 (standard deviation, 2.5) (median, 2.0; interquartile range, 1.0−4.0).

Conclusions: In the United States, anti-VEGF injection was the most frequently utilized treatment for mCNV. Those treated were observed to gain vision. However, one quarter of patients received no treatment and lost vision. Further studies are needed to understand the sociodemographic and health-systems barriers surrounding the delivery of anti-VEGF injections to patients with mCNV. *Ophthalmology 2017;124:935-943 © 2017 by the American Academy of Ophthalmology*

Myopic choroidal neovascularization (mCNV) is a rare, vision-threatening complication of myopia. Patients who develop mCNV can present with an acute deterioration of central visual acuity (VA) and have a high risk of long-term vision loss if they are not promptly treated.[1−7] Though there are many theories behind the pathogenesis of mCNV, the typical course is progressive and excessive elongation of the anterior−posterior axis of the globe that causes mechanical stress on the retina, resulting in breaks in the Bruch membrane and the formation of abnormal vessels in the subretinal space.[1,4]

To date, the treatment options for mCNV in the United States (U.S.) include intravitreal anti-VEGF injections (i.e., bevacizumab/ranibizumab/aflibercept), verteporfin photodynamic therapy (vPDT), and laser photocoagulation.[8] In the U.S., ranibizumab was approved in January 2017 for the treatment of mCNV; outside of the U.S., ranibizumab and aflibercept are approved in certain countries.[9−11] Additionally, in the U.S., vPDT is approved for the treatment of subfoveal mCNV. Although studies report the benefits of these therapies for mCNV, there are few national-level data on the treatment patterns and outcomes for mCNV in the U.S.[12−15] Specifically, there are limited data on the type and promptness of treatment that ophthalmologists offer to their patients with mCNV. Furthermore, for patients treated with anti-VEGF injections, few data exist on injection frequency and visual outcomes. To address these knowledge gaps, we used the American

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Academy of Ophthalmology's IRIS (Intelligent Research in Sight) Registry, the nation's first comprehensive eye disease clinical registry, to characterize treatment patterns and outcomes for mCNV in the U.S. The primary aims of this study were to assess the initial treatment offered to treatment-naïve mCNV patients and related visual outcomes; to estimate the timing of anti-VEGF administration in treatment-naïve mCNV patients; and to evaluate the burden of anti-VEGF injections and office visits experienced by treatment-naïve mCNV patients. The secondary aim of this study was to assess factors associated with the above management patterns for treatment-naïve mCNV patients.

Methods

Study Population

To identify individuals with myopic CNV in the U.S., we used data from the American Academy of Ophthalmology's IRIS Registry, the nation's first comprehensive eye disease clinical registry. The IRIS Registry is a centralized data repository that collects data on real-world practice patterns via electronic health records from ophthalmology practices across the U.S. Sociodemographic data (age, sex, race, geographic location of residence) were collected on individuals 18 years of age and older. Additionally, we obtained data on the patient's refraction (right eye) and presenting VA (Snellen format). Data were collected during the period from January 1, 2012 to December 31, 2014. In the sample of practices analyzed for this study, there was no identification at the patient level to determine whether the same patient was seen in different practices during the same time period. However, based on the recorded age, sex, and other sociodemographic characteristics of individuals in our study sample, no individual had the same characteristics, making it unlikely that we analyzed the same patient multiple times in our study.

Ethics

Data from the IRIS Registry are de-identified and do not require patient-level consent. Participating providers in the IRIS Registry reported their encounters on every patient seen in their practices. All diagnoses attached to a patient in the electronic health records represent a legal medical record and represent real-world diagnostic patterns.

Evaluation of Treatment-Naïve Myopic Choroidal Neovascularization Patients

As previously described, patients were defined as having mCNV if they had a high myopic refraction (myopia worse than or equal to −6 diopters in spherical equivalence, right eye) and an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code of "Retinal Neovascularization NOS" (ICD-9-CM 362.16), which reflects the presence of subretinal or choroidal neovascularization that did not have sufficient evidence to be associated with other specific retinal diagnoses (i.e., exudative age-related macular degeneration).[5] To ensure that our study population had underlying pathologic myopia, we only included those who had at least 1 of the ICD-9-CM diagnoses indicating "Progressive High (Degenerative) Myopia" (ICD-9-CM 360.21) at any point during their ophthalmic care. The first recorded date of the ICD-9-CM code of "Retinal Neovascularization NOS" during the study period of January 1, 2012, to December 31, 2014, was defined as the index date.

To ensure that the selected patients were treatment-naïve, newly diagnosed mCNV patients, we selected individuals who had at least 365 days of eligibility before the index date with no recorded mCNV diagnosis or procedural treatment for a choroidal neovascular membrane (i.e., CPT 67221/67225/67220/67028, representing focal laser, anti-VEGF, or PDT) before the index date. Individuals ever noted to have any other retinal condition possibly requiring anti-VEGF treatment, such as exudative age-related macular degeneration, diabetic macular edema, or retinal vein occlusion, were also excluded. Thereafter, we only included patients who had at least 365 days of follow-up data after the index date to ascertain treatment patterns for at least a full year after the index date. Analyses were conducted on individuals with complete VA data.

Evaluation of Initial Myopic Choroidal Neovascularization Treatment

The type of initial treatment for mCNV was defined as the administration of 1 of the following within the first 365 days of the index date: (1) observation (i.e., no treatment); (2) intravitreal anti-VEGF injection; (3) vPDT; or (4) laser photocoagulation. Intravitreal anti-VEGF (i.e., bevacizumab, ranibizumab, aflibercept, or pegaptanib) was identified through the CPT code 67028. Photodynamic therapy (PDT) was identified through the CPT code 67221 or 67225. Laser photocoagulation was identified through the CPT code 67220 or 0117T. When a patient did not receive anti-VEGF, PDT, or laser photocoagulation during the first year after the index date, we categorized these individuals as being observed. Combination treatment with the above therapies was also assessed. "Any treatment" was defined as the administration of intravitreal anti-VEGF, PDT, or laser photocoagulation.

Evaluation of Visual Acuity

VA was recorded in Snellen format. For analysis, we converted VA to logMAR units. VA for the affected eye on the index date was used as the baseline value. VA from the visit closest to 1 year after the index date (within 3 months) was used for the 1-year post−index date VA. No individuals had 1-year post−index date VA more than 15 months after the index date.

Evaluation of Timing of Initial Anti-VEGF Injection Administration

Among those receiving anti-VEGF injections, "delayed treatment" was defined as anti-VEGF injection that was given more than 1 month (i.e., >30 days) after the index date. "Prompt treatment" was defined as anti-VEGF injection that was given within a month (≤30 days) of the index date.

Evaluation of Number of Office Visits

Office visit frequency was assessed by evaluating the number of actual office records uploaded to the IRIS Registry. When individuals with treatment-naïve mCNV were seen at the index date and not subsequently seen for at least 365 days, they were classified as having "limited follow-up." In analyses, we compared the characteristics of those with only 1 visit (i.e., "limited follow-up") relative to those who had 2 or more visits during the first 365 days after the index date. To assess the proportion of mCNV patients that were closely followed by retina specialists, we estimated the proportion of patients being seen on a monthly (i.e., 4 weeks ±7 days) basis for 3, 6, and 12 consecutive months.

Evaluation of Anti-VEGF Injection Burden

Anti-VEGF injection burden for a given eye with mCNV was estimated by calculating the total number of injections per affected eye among those with at least 1 anti-VEGF injection over the first year after the index date. We assessed injection frequency among individuals with unilateral disease. Bilateral mCNV disease was defined when (1) there was evidence of bilateral intravitreal injections (CPT 67028-50), or (2) there was evidence of both CPT codes 67028-LT (i.e., intravitreal injection left eye) and 67028-RT (i.e., intravitreal injection right eye) within 365 days of the index date, or (3) there were 2 or more intravitreal injections (CPT 67028) within a 15-day period at any point during the follow-up period.

Statistical Analysis

Group differences were assessed by using chi-square analyses, *t* tests, or analysis of variance, as appropriate. When the data did not follow a normal distribution, nonparametric methods (i.e., Wilcoxon signed rank test) were utilized. Regression analyses were conducted to assess whether treatment outcomes were associated with underlying socio-demographic or ocular factors. Multivariable logistic regression analyses were used to assess factors associated with the administration of anti-VEGF injections vs. observation, while adjusting for the potential impact of age, sex, race/ethnicity, geographic residence, insurance status, baseline VA, and the degree of myopia. We also assessed factors associated with limited follow-up of patients diagnosed with treatment-naïve mCNV. In this logistic regression model, the covariates were similar to that in the first model, but we also included an independent variable describing the presence of anti-VEGF injection that was given within the first month of the index date. In both of the regression models, interactions were assessed among sex, age, race, myopia status, and baseline VA and were presented in the model only if they were significant.

For each treatment group, changes in VA 1 year after the index date were calculated by assessing the mean difference in logMAR VA between that recorded on the index date and that recorded 1 year post-index date. Because the distribution of change in VA did not follow a normal distribution, a Wilcoxon signed rank test was used to assess if the visual changes were significantly improved or diminished from baseline.

All data were analyzed using Stata 14 (StataCorp LP, College Station, TX).[16]

Results

A total of 61 251 individuals were identified in the IRIS Registry during the study period of January 1, 2012, to December 31, 2014. Among these individuals, after applying the exclusion criteria, 211 individuals were identified as having treatment-naïve mCNV (Fig 1). Specifically, 56 039 (91.5%) individuals were excluded because they had no mCNV diagnosis by a retinal specialist (RS); 3380 (5.5%) individuals were excluded because they did not have at least 365 days of eligibility in the IRIS dataset before the index date; 306 (5.0%) were excluded because they did not have at least 365 days of follow-up in the IRIS Registry after the index date; 835 (1.4%) individuals were excluded because they did not have a second confirmatory mCNV diagnosis after the index date; 186 (0.3%) individuals were excluded because they had a prior recorded treatment for choroidal neovascularization; 182 (0.3%) individuals were excluded because there was never a recorded diagnosis of progressive (high) myopia; and 112 (0.2%) individuals were excluded because they had a recorded diagnosis of another major retinal condition (i.e., exudative age-related macular degeneration, retinal vein occlusion, or diabetic macular edema) requiring anti-VEGF treatment. Of the 211 treatment-naïve incident mCNV patients, 185 (87.7%) had sufficient VA data for analysis (Fig 1).

Patients with complete VA data were significantly more likely to have been treated with anti-VEGF treatment (72.4% vs. 26.9%, $P < 0.01$) and seen more frequently in the physician's office (3.3 vs. 1.6 visits/year, $P < 0.01$) than those with incomplete data (Table 1). Among the 185 individuals with complete VA data, 53.5% (99/185) and 46.5% (86/185) had mCNV in the right and left eye, respectively. Additionally, among those with complete VA data, 40.0% (74/185) had a record of anti-VEGF injections for only 1 eye, 32.4% (60/185) were given anti-VEGF injections for both eyes, and 27.0% (50/185) were observed; and 1 person (0.5%) was given vPDT during the first year after the index date (Fig 1).

Initial Treatment for Treatment-Naïve Myopic Choroidal Neovascularization Patients

Among all treatment-naïve mCNV patients in the U.S., treatment within 1 year was documented for 73.0% (135/185) and 27.0% (50/185) were observed (i.e., no documented treatment) for at least 1 year after the index date. Of those with documented treatment, 99.3% (134/135) received anti-VEGF injections and 0.7% (1/135) received vPDT as their initial treatment. Among those receiving anti-VEGF injections, 55.2% (74/134) had anti-VEGF injections for unilateral disease and 44.8% (60/134) required anti-VEGF injections for bilateral disease. No individual received laser photocoagulation or combination therapy (i.e., anti-VEGF plus vPDT).

In our multivariable model, we found that the odds of female subjects receiving anti-VEGF treatment were 71% lower than for male subjects (adjusted odds ratio [AOR], 0.29, 95% confidence interval [CI] 0.11−0.76, $P = 0.01$). The odds of receiving anti-VEGF treatment were significantly lower among older individuals (AOR, 0.96 per year of age; 95% CI, 0.94−0.99; $P = 0.006$) and among those with higher myopic refraction (AOR, 0.68 per diopter worsening in myopic refraction; 95% CI, 0.58−0.80; $P < 0.01$). Conversely, the odds of receiving anti-VEGF injection were significantly greater among those with worse baseline VA (AOR, 3.02 per 0.3 logMAR unit change [i.e., worsening VA]; 95% CI, 1.83−4.94; $P < 0.01$) (Table 2).

Visual Acuity Changes 1 Year after Index Date

Among those with treatment-naïve mCNV who were ever given an anti-VEGF injection, the 1-year post−index date logMAR VA (logMAR, 0.32; 95% CI, 0.25−0.40) was significantly better than the logMAR VA at the index date (logMAR, 0.49; 95% CI, 0.41−0.57), translating to an improvement in Snellen VA from ~20/60 to ~20/40. More specifically, among those who received anti-VEGF injections during the first year after diagnosis, the mean logMAR VA improvement was 0.17 units (95% CI, 0.12−0.20; $P < 0.01$). In comparison, among those who were observed (not treated), the logMAR VA 1-year post−index date (logMAR, 0.39; 95% CI, 0.28−0.50) was worse than that from the index date (logMAR, 0.36; 95% CI, 0.24−0.48), translating to an overall mean decline in Snellen VA from ~20/45 to ~20/50. Specifically, among those that were "observed" (not treated), there was a mean logMAR VA decline of 0.031 units (95% CI, 0.0075−0.054; $P < 0.01$) (Fig 2). In the 1 patient who was given vPDT, the logMAR VAs on the index date and 1-year post−index date were 0.40 and 0.40 (both, Snellen equivalent, 20/50), respectively.

The proportion of treatment-naïve mCNV patients who gained 0.20 logMAR units or more (equivalent to 2 or more Snellen lines)

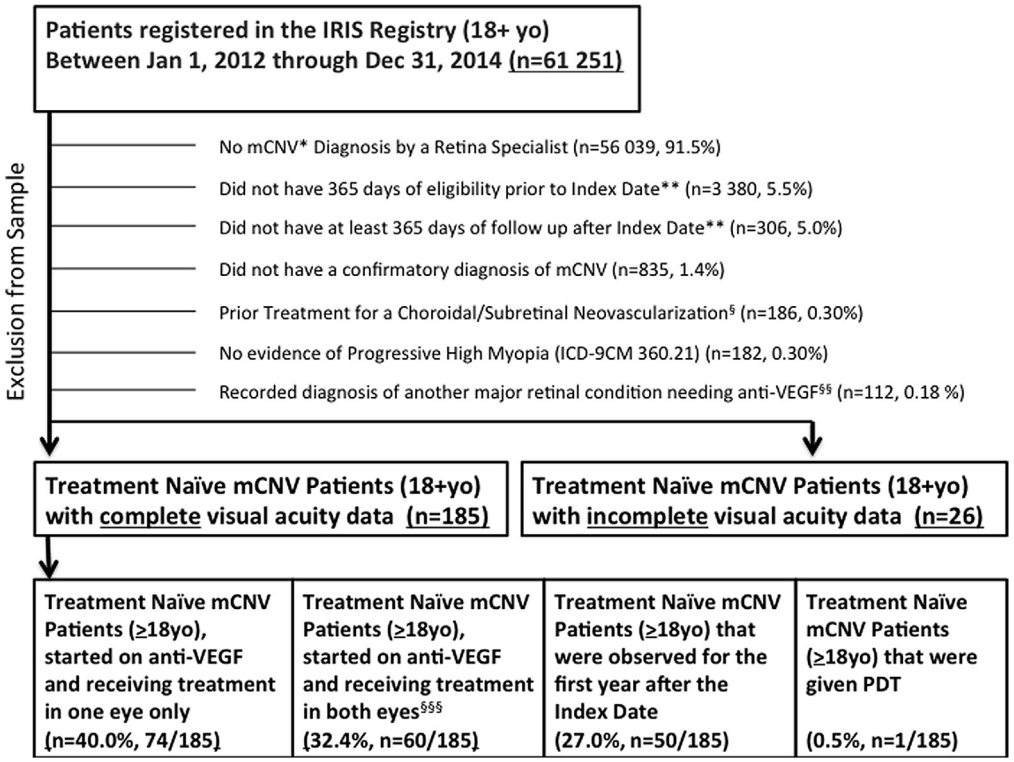

Figure 1. Sample plan for the analysis of treatment patterns around myopic choroidal neovascularization in the United States: analysis of the IRIS Registry 2012–2014. *Diagnosis of myopic choroidal neovascularization (mCNV) based on patients coded as retinal neovascularization NOS (i.e., ICD-9-CM 362.16) and with a high myopic refraction (i.e., myopia worse than or equal to −6 diopters in spherical equivalence, right eye). **Index date defined as the first recorded date of the ICD-9-CM code of retinal neovascularization NOS during the study period of January 1, 2012, to December 31, 2014. §Any recorded treatments for choroidal/subretinal neovascularization (CPT 67221/67225/67220/67028) any time before the index date. §§Excludes individuals with a recorded diagnosis of major retinal conditions that could be treated with anti-VEGF treatment, including (1) exudative age-related macular degeneration (362.52), (2) diabetic macular edema (362.07), or (3) retinal vein occlusion (362.35 or 362.36) at any point during the study period (i.e., 365 days before the index date, date of index date, 365 days after the index date). §§§Excludes patients that have any evidence of receiving anti-VEGF treatment in BOTH EYES within the 365 days of the initial diagnosis date (i.e., index date) of mCNV. Specifically, (1) excludes individuals with CPT codes 67028–67050 (i.e., bilateral intravitreal injections), (2) excludes individuals who have both CPT codes of 67028-LT (i.e., intravitreal injection left eye) and 67028-RT (i.e., intravitreal injection right eye) within the 365 days after the initial diagnosis date (i.e., index date), (3) excludes individuals that received 2 or more intravitreal injections (67028) within a 15-day period at any point during the reporting period. CPT = current procedural/procedure terminology; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; IRIS = Intelligent Research in Sight; NOS = not otherwise specified; VEGF = vascular endothelial growth factor.

at the 1-year post–index point was significantly greater among those given anti-VEGF therapy (37.3%, 50/134) than in those "observed" (not treated) (0%, 0/50) ($P < 0.01$). Among those given anti-VEGF therapy, the proportion who gained more than 0.20 logMAR units tended to be higher among those who received treatment within 30 days (40.9%, 45/110) than in those who received treatment after 30 days (20.8%, 5/24) ($P = 0.07$).

Promptness of Initial Anti-VEGF Injection Administration for Treatment-Naïve Myopic Choroidal Neovascularization Patients

Among those treatment-naïve mCNV patients that ever received an anti-VEGF injection, the mean number of days to anti-VEGF treatment was 33.1 (±79.6) days (median, 0 days; range, 0–326 days). A total of 17.9% (24/134) had "delayed treatment" (more than 30 days after the index date). In multivariable analysis, "delayed treatment" was not significantly associated with age, race, sex, insurance, geographic location, baseline VA, or myopic refraction (data not shown).

Frequency of Office Visits for Treatment-Naïve Myopic Choroidal Neovascularization Patients

The mean (± standard deviation [SD]) number of office visits recorded for treatment-naïve mCNV patients during the first year after the index date was 3.3 (±3.0; median, 2.0; range, 1–19). The mean number of visits was significantly greater among those who received anti-VEGF injections (4.1±3.2; median, 3.0; range, 1–19) than among those who were observed (no treatment) (1.0±0.1; median, 1.0; range, 1–2; $P < 0.01$). The mean number of office visits among those with unilateral mCNV disease and bilateral mCNV disease was 3.58 (±2.47) and 4.76 (±3.78), respectively ($P = 0.03$). The 1 individual given PDT had only 1 visit during the first 365 days after diagnosis. Among all treatment-naïve mCNV patients, 10.8% (20/185), 2.7% (5/185), and 0.5% (1/185) were seen on a monthly basis over 3 months, 6 months, and 12 months, respectively.

The proportion of individuals who had "limited follow-up" after the index date (i.e., only seen once within a 1-year period) was significantly higher among those who were observed (98.0%)

Table 1. Characteristics of Adult Americans Diagnosed with Treatment-Naïve Myopic Choroidal Neovascularization with Incomplete vs. Complete Visual Acuity Data, IRIS Registry 2012–2014

	Incomplete Data* (N = 26)	Complete Data (N = 211)	P Value
Age (years), mean (SD)	56.1 (±20.0)	55.8 (±15.8)	0.92
Female, n (%)	20 (76.9%)	128 (69.2%)	0.42
Race, n (%)			0.84
White	14 (52.9%)	105 (56.8%)	
Black	1 (3.9%)	14 (7.6%)	
Asian	2 (7.7%)	11 (6.0%)	
Other/unknown	9 (33.6%)	55 (29.7%)	
Geographic residence, n (%)			0.99
Northeast	6 (23.1%)	39 (21.1%)	
South	11 (42.3%)	79 (42.7%)	
Midwest	4 (15.4%)	31 (16.8%)	
West	5 (19.2%)	36 (19.5%)	
Presence of health insurance, n (%)	20 (76.9%)	125 (67.6%)	0.33
Myopia status (diopter), mean (SD)	−10.4 (±5.1)	−10.0 (±4.5)	0.71
Initial treatment type, n (%)			<0.01
Observation	19 (73.1%)	50 (27.0%)	
Anti-VEGF	7 (26.9%)	134 (72.4%)	
Laser	0 (0.0%)	0 (0.0%)	
PDT	0 (0.0%)	1 (0.5%)	
LogMAR visual acuity at index, mean (SD)	N/A	0.50 (±0.71)†	N/A
Office visits (n), mean (SD)	1.6 (±1.4)	3.3 (±3.0)	<0.01

logMAR = logarithm of the minimal angle of resolution; N/A = not applicable; PDT = photodynamic therapy; SD = standard deviation; VEGF = vascular endothelial growth factor.
*Individuals were considered to have incomplete data if they had incomplete visual data on the date of myopic choroidal neovascularization diagnosis.
†Snellen equivalent of ~20/50.

than in those who had anti-VEGF treatment (9.7%) ($P < 0.01$) (Table 3). Multivariable logistic regression analysis showed that factors significantly associated with a lower odds of limited follow-up included the initiation of anti-VEGF (AOR, 0.00029; 95% CI, 0.000015–0.0057; $P < 0.01$), female sex (AOR, 0.14; 95% CI, 0.03–0.65; $P = 0.01$), and worse baseline VA (AOR, 0.34 per 0.3 logMAR unit; 95% CI, 0.13–0.91; $P = 0.03$) (Table 2).

Table 2. Factors Associated with the Management of Treatment-Naïve Myopic Choroidal Neovascularization Patients in the United States: Analysis of the IRIS Registry 2012–2014

		Treatment-Naïve mCNV Patients	
	Interval	*Treatment with Anti-VEGF vs. Observation, Adjusted Odds Ratio (95% CI) N = 184**	*Limited Office Follow-up after Diagnosis,† Adjusted Odds Ratio (95% CI) N = 185*
Age (years)	Per year	0.96‡ (0.94–0.99)	1.02 (0.98–1.07)
Female	Vs. male	0.29‡ (0.12–0.76)	0.14‡ (0.03–0.65)
Race			
Black	Vs. white	0.23‡ (0.06–0.87)	0.75 (0.07–8.58)
Asian	Vs. white	0.76 (0.16–3.71)	0.92 (0.0018–468.2)
Other/Unknown	Vs. white	0.92 (0.37–2.27)	0.11 (0.0091–1.27)
Geographic residence			
South	Vs. Northeast	1.06 (0.38–2.93)	0.34 (0.060–2.02)
Midwest	Vs. Northeast	0.90 (0.25–3.25)	1.00 (0.13–7.68)
West	Vs. Northeast	0.86 (0.26–2.86)	0.69 (0.11–4.34)
Health insurance	Vs. no insurance	0.84 (0.35–2.01)	2.03 (0.41–10.0)
Myopic refraction	Per negative diopter	0.68‡ (0.58–0.80)	1.18 (0.87–1.59)
LogMAR visual acuity at index	Per 0.3 logMAR units	3.00‡ (1.83–4.94)	0.34‡ (0.13–0.91)
Anti-VEGF treatment	Vs. no anti-VEGF Tx	N/A	0.00029‡ (0.0000015–0.0057)

CI = confidence interval; logMAR = logarithm of the minimal angle of resolution; mCNV = myopic choroidal neovascularization; N/A = not applicable; Tx = treatment; VEGF = vascular endothelial growth factor.
*One individual who received photodynamic therapy was excluded from this analysis.
†Dichotomous variable comparing those with only 1 visit relative to those that had ≥2 visits during the first year after the index date.
‡$P < 0.05$.

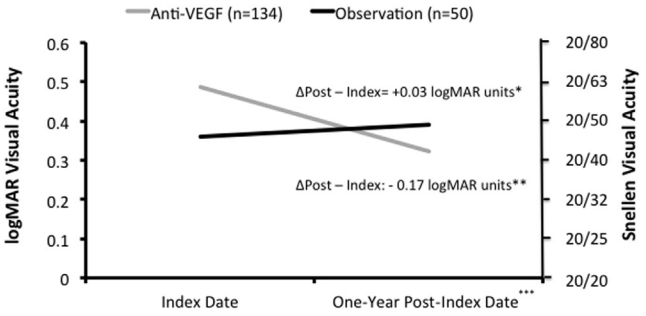

Figure 2. Change in logMAR visual acuity among treatment-naïve myopic choroidal neovascularization patients by type of treatment: Analysis of the IRIS Registry 2012–2014. *Change in logMAR visual acuity (i.e., 1-year post–index date visual acuity relative to index date visual acuity) among those who were observed during the first 365 days after diagnosis: +0.03 units (95% confidence interval 0.01, 0.05) ($P < 0.01$ based on signed rank test) (worsening in Snellen acuity: ~20/45 → ~20/50). **Change in logMAR visual acuity (i.e., 1 year post–index date visual acuity relative to index date visual acuity) among those who were given anti-VEGF injections during the first 365 days after diagnosis: −0.18 units (95% confidence interval −0.21, −0.12) ($P < 0.01$ based on signed rank test) (improvement in Snellen visual acuity: ~20/60 → ~20/40). ***Mean duration to 1-year post–index date: anti-VEGF injections group (386.6±13.7 days) vs. observation group (378.4±7.5 days) ($P < 0.01$). IRIS = Intelligent Research in Sight; logMAR = logarithm of the minimal angle of resolution; VEGF = vascular endothelial growth factor.

Anti-VEGF Injection Burden for Treatment-Naïve Unilateral Myopic Choroidal Neovascularization

Among those with treatment-naïve unilateral mCNV who were given an anti-VEGF injection, the mean number of injections during the first year after the index date was 2.8 (SD, ±2.5; median, 2; interquartile range, 1–4) (Fig 2). The mean number of administered injections did not differ between male (2.7±2.7) and female subjects (2.8±2.4) ($P = 0.91$) (Fig 3). Additionally, the proportion of treatment-naïve unilateral mCNV patients that received 3, 6, and 12 injections over a 3-month, 6-month, and 12-month period was 16% (12/74), 1% (1/74), and 0% (0/74), respectively.

Discussion

In the U.S., practice patterns among RSs indicate that intravitreal anti-VEGF injection was the most frequently utilized treatment for mCNV, and visual gains were observed in this group of patients. Yet many patients were also observed and not seen frequently; these patients were observed to experience further vision loss, albeit mild. When RSs initiated anti-VEGF treatment for mCNV patients, they typically administered it within 30 days of diagnosis. On average, treated patients received 3 injections during the first year after diagnosis. To our knowledge, our work represents a large-scale population-based study to examine practice patterns for mCNV among RSs in the U.S. This study also demonstrates the feasibility of utilizing national registries such as the IRIS Registry to evaluate patient care in the real-world setting and compare the outcomes with those seen in clinical trials.

Previous work has shown that intravitreal anti-VEGF injection is an effective treatment modality for mCNV and that patients show significant visual improvement. Specifically, several studies with at least 1 year of follow-up have shown that the VA of those treated with anti-VEGF improved 2 lines or more, consistent with this study.[17–20] However, the visual outcome gains we observed were slightly lower than those reported by the RADIANCE Trial, which described a nearly 3-line gain (~14 letter gain) in VA among treatment-naïve mCNV patients receiving ranibizumab.[13] This difference likely reflects the systematic differences between patients followed in the real world vs. those evaluated monthly in a clinical trial setting, Furthermore, the VA of those in the IRIS Registry may not represent best-corrected VA; the type of CNV in the IRIS Registry may not be macula-involving, as defined in the RADIANCE Trial; and follow-up in the IRIS Registry was less frequent than in a clinical trial setting, all of which could lead to potentially worse visual outcomes in the real-world setting. Nevertheless, it is important to realize that anti-VEGF injection in the real-world setting does lead to significant visual improvement among treatment-naïve mCNV patients, especially if given promptly.

Prior studies have shown that mCNV patients treated with anti-VEGF injections required fewer injections over a 12-month period than did those with CNV secondary to age-related macular degeneration. The RADIANCE trial showed that the median number of ranibizumab injections during the first 12 months among those in the "Treatment Guided by Visual Acuity Stabilization Criteria Group (Group 1)" and those in the "Treatment Guided by Disease Activity Criteria Group (Group 2)" was 4.0 and 2.0, respectively.[13] The mean number of injections for groups 1 and 2 in the RADIANCE trial was 4.6 and 3.5, respectively.[13] These results were slightly higher than that seen in our study, where the median and mean number of anti-VEGF injections was 2.0 and 3.0, respectively. Yet the number of injections we observed was higher than that reported by Nakanishi et al., who noted that the mean number of injections was 1.35 over a 1-year period.[21] Although the small discrepancies here could be attributed to differences in the types of patients studied or clinical trial protocols, it is clear that those with mCNV in the real-world setting received fewer injections than those with CNV secondary to age-related macular degeneration; the CATT trial[22] estimated 12 to 14 injections of ranibizumab or bevacizumab over a 2-year period, and a clinic-based study by Holekamp et al[23] estimated a mean annual number of 4.7 bevacizumab or 5.0 ranibizumab injections for the treatment of exudative age-related macular degeneration.

Our study also showed that RSs in the U.S. were more likely to treat mCNV patients with worse VA, while observing those with relatively good VA for at least 1 year. Given that our study period occurred when anti-VEGF injections were not yet approved for treatment for mCNV in the U.S., the decision to observe could have been related to a greater perceived risk of off-label anti-VEGF treatment compared with the possible benefit of visual gains. The decision to observe could perhaps stem from the belief that mCNV may spontaneously involute or that the CNV was deemed to be in an extrafoveal location

Table 3. Characteristics of Treatment-Naïve Myopic Choroidal Neovascularization Patients by Type of Initial Treatment: Analysis of the IRIS Registry 2012–2014

	Type of Initial Treatment Administered for mCNV*		
	Observation† *(N = 50)*	*Anti-VEGF*‡ *(N = 134)*	P *Value*
Age (years), mean (SD)	58.5 (18.1)	54.8 (14.9)	0.16
Sex, n (%)			0.05
Male	10 (20.0%)	47 (35.1%)	
Female	40 (80.0%)	87 (64.9%)	
Race, n (%)			0.13
White	26 (52.0%)	78 (58.2%)	
Black	6 (12.0%)	8 (6.0%)	
Asian	4 (8.0%)	7 (5.2%)	
Other/unknown	14 (28.0%)	41 (30.6%)	
Geographic residence, n (%)			0.98
Northeast	10 (20.0%)	29 (21.6%)	
South	22 (44.0%)	57 (42.5%)	
Midwest	9 (18.0%)	22 (16.4%)	
West	9 (18.0%)	26 (19.4%)	
Presence of health insurance, n (%)	35 (70.0%)	90 (67.2%)	0.71
Myopia status (diopter), mean (SD)	−11.2 (±5.3)	−9.6 (±4.1)	0.04
LogMAR visual acuity at index, mean (SD)	0.36 (0.42)	0.49 (0.46)	0.09
Office visits (n), mean (SD)	1.02 (0.13)	4.11 (3.17)	<0.01
Limited follow-up,§ n (%)	49 (98.0%)	13 (9.7%)	<0.01

CPT = current procedural/procedure terminology; ICD-9-CM = International Classification of Diseases Ninth Revision Clinical Modification; IRIS = Intelligent Research in Sight; logMAR = logarithm of the minimal angle of resolution; mCNV = myopic choroidal neovascularization; PDT = photodynamic therapy; SD = standard deviation; VEGF = vascular endothelial growth factor.
*Diagnosis of mCNV based on patients coded as Retinal Neovascularization NOS (i.e., ICD-9-CM 362.16) and with a high myopic refraction (i.e., myopia worse than or equal to −6 diopters in spherical equivalence, right eye).
†Observation defined as lack of administration of anti-VEGF, PDT, or laser photocoagulation.
‡Intravitreal anti-VEGF (i.e., bevacizumab, ranibizumab, aflibercept) was identified through CPT code 67028. PDT was identified through CPT code 67221 or 67225. Laser photocoagulation was identified through CPT code 67220 or 0117T. No patient in the study sample received laser photocoagulation. One patient in the study received PDT.
§Defined as individuals with treatment-naïve mCNV that were only seen once on the index date and not subsequently seen within a 1-year period.

that did not require treatment.[24] Although our study was unable to confirm any spontaneous involution of mCNV or the location of the CNV, we showed that patients with good baseline VA had a slight visual decline a year after diagnosis. Though this may suggest that observation for those with good vision may be a viable option during the first year of mCNV diagnosis, physicians/patients should understand that chronically untreated eyes were associated with visual decline.[2,3]

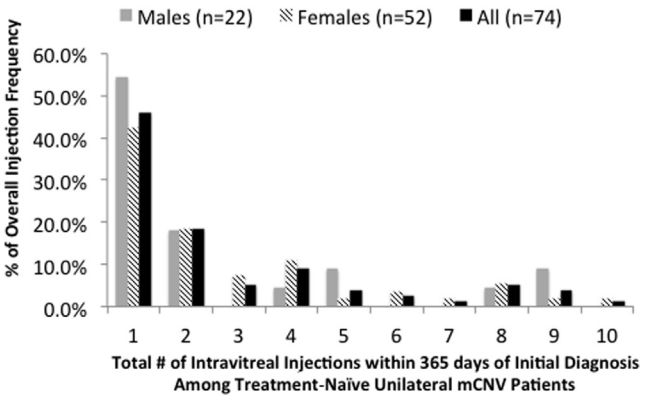

Figure 3. Intravitreal anti-vascular endothelial growth factor (VEGF) injection burden among treatment-naïve unilateral myopic choroidal neovascularization (mCNV) patients started on anti-VEGF therapy during the first 365 days after diagnosis. Note: Mean number of total injections during the first year after the index date was 2.8 (standard deviation, ±2.5; median, 2; interquartile range, 1–4). The mean number of administered injections did not differ between male (2.7±2.7) and female subjects (2.8±2.4) ($P = 0.91$).

Patient factors that were associated with the RS's decision to observe (i.e., not treat) the mCNV lesion included female sex, older age, and higher myopic refraction. The lack of anti-VEGF treatment for female subjects may have been due to physician hesitation to treat women of reproductive potential with a medication that had not yet been approved by the U.S. Food and Drug Administration, although this is unlikely given that the mean age of women in our sample was 55 years old. The lower treatment rate in more myopic individuals could perhaps be related to these individuals being perceived as having lower visual potential, given the greater rate of underlying retinal atrophy, photoreceptor degeneration, and/or other coexisting retinal pathology.[25] Given the potential benefit of anti-VEGF injections for mCNV, future research is needed to better understand the health system or socioeconomic barriers that limit the administration of anti-VEGF injections. Additionally, it is important to realize that our study showed that U.S. retinal specialists very rarely utilized vPDT for the treatment of mCNV, perhaps because of the destructive nature of this treatment modality.[26]

Our study also showed that the frequency of office visits during the first year after diagnosis was low (median visit of 1.0) among mCNV patients who were observed and not treated with anti-VEGF injections. Although the specific reasons for this lack of follow-up are not clear, we found that male subjects and those with good vision were more likely to have limited follow-up than their counterparts. It is possible that RSs treating those with good vision may not have felt an urgency to more routinely see patients with good vision. Alternatively, it is possible that the patients themselves did not see the need to follow up with their physician, given their good vision. Regardless, given that mCNV patients have a high risk of developing CNV in the contralateral eye as well as experiencing other pathologic conditions related to their myopia (i.e., retinal tears or detachments), they should be monitored on a routine basis even when active treatment is not pursued at the initial visit. Future research is needed to better understand health system or socioeconomic barriers that may limit patients from being seen on a more regular basis.

The limitations of the data from the IRIS Registry included the following: 12.3% of the eligible individuals had missing data; the method of diagnosing and recording the presence and type of mCNV (i.e., subfoveal vs. juxtafoveal vs. extrafoveal) was not reported or standardized across treating physicians; and the subjective/objective reasons behind the treatment decisions could not be discerned based on electronic health record data. Given that those with incomplete data were more likely to have been observed, the actual prevalence of individuals being observed for treatment-naïve mCNV in the real-world setting may be higher. Also, our diagnostic method of mCNV is based on a proxy and may actually represent choroidal neovascularization secondary to other causes, such as ocular histoplasmosis, angioid streaks, and uveitic conditions. Yet we believe that, based on our very stringent inclusion/exclusion criteria, those included in this study actually had mCNV rather than CNV from another cause. Conversely, it is possible that physicians are coding mCNV as another diagnosis, such as exudative age-related macular degeneration, to circumvent insurance issues for treatment reimbursement. Such practice habits could lead to a misclassification bias in which our study results would be an underestimate of the true treatment rate of mCNV in the U.S. Furthermore, given that the IRIS Registry represents real-world practice patterns, critics may question the data reliability. To address this issue, we applied stringent inclusion/exclusion criteria in selecting our study population so that we were confident that our study population had treatment-naïve mCNV with appropriate treatment and VA data. Consequently, there may be a selection bias, where our study population may represent treatment patterns by a group of RSs that are more meticulous with their data collection processes.

Another study limitation was that our data focused on treatment patterns over a 1-year period, limiting our insight into the longer-term history of mCNV according to how it was managed. Finally, it is possible that those who were categorized as being observed were actually referred to an outside ophthalmologist for treatment, leading us to underestimate the treatment prevalence. However, this is unlikely given that we selected for individuals who were under the care of RSs, a group that has received training in the diagnosis and management of this condition, and not likely to refer these patients to another specialist.

In summary, this study utilizes a large ophthalmic registry, the IRIS Registry, to describe practice patterns for mCNV in the U.S. We found that in the U.S., the majority of treatment-naïve mCNV patients received only a few anti-VEGF injections and subsequently experienced significant visual gains. However, about one quarter of treatment-naïve mCNV patients were observed for at least 1 year after the diagnosis, possibly putting them at risk for further vision loss. Further studies are necessary to elucidate the reasons behind why retina specialists may defer treating patients with mCNV. Finally, the use of the IRIS Registry could be a novel tool in identifying areas of unmet need in ophthalmic care and validating the results of ophthalmic clinical trials in the real-world setting. Future studies can further explore the utility of the IRIS Registry as a tool to enhance our understanding of treatment patterns and unmet needs in the management of other devastating ophthalmic conditions.

References

1. Ikuno Y, Jo Y, Hamasaki T, Tano Y. Ocular risk factors for choroidal neovascularization in pathologic myopia. *Invest Ophthalmol Vis Sci*. 2010;51(7):3721-3725.
2. Ohno-Matsui K, Yoshida T. Myopic choroidal neovascularization: natural course and treatment. *Curr Opin Ophthalmol*. 2004;15(3):197-202.
3. Wong TY, Ferreira A, Hughes R, et al. Epidemiology and disease burden of pathologic myopia and myopic choroidal neovascularization: an evidence-based systematic review. *Am J Ophthalmol*. 2014;157(1):9-25.e12.
4. Wong TY, Ohno-Matsui K, Leveziel N, et al. Myopic choroidal neovascularisation: current concepts and update on clinical management. *Br J Ophthalmol*. 2015;99(3):289-296.
5. Willis JR, Vitale S, Morse L, et al. The prevalence of myopic choroidal neovascularization in the united states: analysis of the IRIS® Data Registry and NHANES. *Ophthalmology*. 2016;123(8):1771-1782.
6. Curtin BJ, Karlin DB. Axial length measurements and fundus changes of the myopic eye. *Am J Ophthalmol*. 1971;71(1 Pt 1):42-53.
7. Grossniklaus HE, Green WR. Pathologic findings in pathologic myopia. *Retina*. 1992;12(2):127-133.
8. American Academy of Ophthalmology. Basic and clinical science course 2016-2017. Section 12: Retina and Vitreous. San Francisco; American Academy of Ophthalmology; 2016.
9. Myopic choroidal neovascularization [media fact sheet]. Basel, Switzerland: Novartis; July 3, 2014. Available at: http://www.novartisalconretina.com/docs/NOVARTI_Myopic_CNV_JULY_2014_1_updated%2009-07-14.pdf. Accessed March 13, 2017.
10. Regeneron announces Eylea® (AFLIBERCEPT) injection for the treatment of patients with myopic choroidal neovascularization (CNV) [news release] Tarrytown, New York: Regeneron Pharmaceuticals; September 22, 2014. Available at: http://investor.regeneron.com/releasedetail.cfm?releaseid=871800. Accessed March 13, 2017.

11. FDA approves Genentech's Lucentis® (Ranibizumab Injection) for myopic choroidal neovascularization [press release]. South San Francisco, California; January 5, 2017. Available at: https://www.gene.com/media/press-releases/14651/2017-01-05/fda-approves-genentechs-lucentis-ranibiz. Accessed March 13, 2017.
12. Claxton L, Malcolm B, Taylor M, et al. Ranibizumab, verteporfin photodynamic therapy or observation for the treatment of myopic choroidal neovascularization: cost effectiveness in the UK. *Drugs Aging*. 2014;31(11):837-848.
13. Wolf S, Balciuniene VJ, Laganovska G, et al. RADIANCE: a randomized controlled study of ranibizumab in patients with choroidal neovascularization secondary to pathologic myopia. *Ophthalmology*. 2014;121(3):682-692.e2.
14. Lalloum F, Souied EH, Bastuji-Garin S, et al. Intravitreal ranibizumab for choroidal neovascularization complicating pathologic myopia. *Retina*. 2010;30(3):399-406.
15. Sakaguchi H, Ikuno Y, Gomi F, et al. Intravitreal injection of bevacizumab for choroidal neovascularisation associated with pathological myopia. *Br J Ophthalmol*. 2007;91(2):161-165.
16. StataCorp. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP; 2015.
17. Ruiz-Moreno JM, Montero JA, Arias L, et al. Twelve-month outcome after one intravitreal injection of bevacizumab to treat myopic choroidal neovascularization. *Retina*. 2010;30(10):1609-1615.
18. Wu PC, Chen YJ. Intravitreal injection of bevacizumab for myopic choroidal neovascularization: 1-year follow-up. *Eye (Lond)*. 2009;23(11):2042-2045.
19. Chan WM, Lai TY, Liu DT, Lam DS. Intravitreal bevacizumab (Avastin) for myopic choroidal neovascularisation: 1-year results of a prospective pilot study. *Br J Ophthalmol*. 2009;93(2):150-154.
20. Ikuno Y, Sayanagi K, Soga K, et al. Intravitreal bevacizumab for choroidal neovascularization attributable to pathological myopia: one-year results. *Am J Ophthalmol*. 2009;147(1):94-100.e1.
21. Nakanishi H, Tsujikawa A, Yodoi Y, et al. Prognostic factors for visual outcomes 2-years after intravitreal bevacizumab for myopic choroidal neovascularization. *Eye (Lond)*. 2011;25(3):375-381.
22. Comparison of Age-related Macular Degeneration Treatments Trials Research Group; Martin DF, Maguire MG, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology*. 2012;119(7):1388-1398.
23. Holekamp NM, Liu Y, Yeh WS, et al. Clinical utilization of anti-VEGF agents and disease monitoring in neovascular age-related macular degeneration. *Am J Ophthalmol*. 2014;157(4):825-833.e1.
24. Avila MP, Weiter JJ, Jalkh AE, et al. Natural history of choroidal neovascularization in degenerative myopia. *Ophthalmology*. 1984;91(12):1573-1581.
25. Curtin BJ, Karlin DB. Axial length measurements and fundus changes of the myopic eye. I. The posterior fundus. *Trans Am Ophthalmol Soc*. 1970;68:312-334.
26. Varano M, Iacono P, Giorno P, et al. Photodynamic therapy in subfoveal and juxtafoveal myopic choroidal neovascularization: a 10-year retrospective analysis. *Ophthalmologica*. 2014;231(4):204-210.

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Abbreviations and Acronyms:
AOR = adjusted odds ratio; **CI** = confidence interval; **CPT** = current procedural/procedure terminology; **ICD-9-CM** = International Classification of Diseases, Ninth Revision, Clinical Modification; **IRIS** = Intelligent Research in Sight; **logMAR** = logarithm of the minimal angle of resolution; **mCNV** = myopic choroidal neovascularization; **NOS** = not otherwise specified; **PDT** = photodynamic therapy; **RS** = retinal specialist; **SD** = standard deviation; **U.S.** = United States; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor; **vPDT** = verteporfin photodynamic therapy.

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