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Evaluation of Patients Receiving Intravitreal Antivascular Endothelial Growth Factor for Diabetic Macular Edema in Clinical Practice in the United States

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Abstract

Purpose: We assessed the effect of treatment frequency with intravitreal antivascular endothelial growth factor (anti-VEGF) agents on visual acuity (VA) in diabetic macular edema (DME). **Methods:** This retrospective analysis assessed electronic medical records of eyes newly diagnosed with DME and treated with an anti-VEGF agent at US clinics using the Vestrum Health (Naperville, Illinois) treatment and outcomes database. Eyes were divided into 2 injection frequency subcohorts ($\leq$ 6 vs > 6 injections/y); treatment frequency and change in mean VA (Early Treatment Diabetic Retinopathy Study letters) were evaluated. **Results:** Among 155 240 eyes assessed, 3028 met inclusion criteria for analysis in year 1 and 1292 in year 2. During year 1 of treatment, 57% (n = 1725) received > 6 injections; most continued to receive the same injection frequency during year 2. Mean VA gain from baseline at year 1 was lower in the $\leq$ 6 than in the > 6 injections/year subcohort (3.7 vs 8.0 letters, respectively; $P <$ .001). Mean VA change from the end of year 1 to year 2 for eyes receiving $\leq$ 6 injections in year 1 generally remained unchanged, irrespective of year 2 dosing frequency. In eyes that received > 6 injections in year 1, mean VA loss was significantly greater for eyes receiving less-frequent dosing in year 2 than in those maintained on > 6 injections. **Conclusions:** More than 50% of eyes with DME in routine clinical practice that completed at least 1 year of follow-up received > 6 injections of an anti-VEGF agent during the first year, resulting in better VA gains than eyes treated less frequently.

Keywords

antivascular endothelial growth factor, bevacizumab, diabetic macular edema, intravitreal aflibercept, ranibizumab, treatment frequency, visual acuity, real-world outcomes

Introduction

Diabetic macular edema (DME) is a major cause of visual impairment in working-aged individuals.[1] Recently, the standard of care for DME has moved from macular laser photocoagulation toward treatment with intravitreal antivascular endothelial growth factor (anti-VEGF) agents, namely United States Food and Drug Administration–approved intravitreal aflibercept injection and ranibizumab, as well as off-label bevacizumab.

Randomized controlled trials have consistently supported the efficacy of consistent intravitreal anti-VEGF injections in improving visual acuity (VA) in patients with DME using either a fixed-dosing schedule or a protocol-defined, flexible-dosing schedule.[2-9] However, these regimens have not been readily adopted in routine clinical practice. Recent evidence suggests that the frequency of anti-VEGF treatments in patients with DME in routine clinical practice may be suboptimal.[10] Understandably, frequent injections can be burdensome for patients and caregivers.[11] However, the extent of the effect of treatment frequency on treatment outcomes in routine clinical practice in the United States is unclear.

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To assess the effect of dosing frequency of intravitreal anti-VEGF agents on visual outcomes in eyes with DME in routine clinical practice, we analyzed electronic medical records from retina specialists in the United States.

Methods

Data Source

Deidentified electronic medical records of eyes with DME in the Vestrum Health treatment and outcomes database (Vestrum Health, Naperville, Illinois) were analyzed. These records were collected from 251 retina specialists at 54 private clinics in the United States and included information about demographics, procedures performed, diseases diagnosed, medications prescribed, and treatment outcomes (eg, VA). Data were extracted from the database using Structured Query Language queries. Institutional review board approval was not sought because it is not generally required for studies such as this in which data collection was in the form of historical deidentified patient electronic health records, which do not affect or influence patient treatment.

Study Population

The study population comprised eyes that were newly diagnosed with DME and were administered their first anti-VEGF injection during the period January 1, 2012, and April 30, 2015. Eyes were included in the study if they had a VA reading on the index date, at month 12, and at least once during each quarter of the study period. VA at month 12 was identified as the reading closest to 12 months following the index date, between months 11 and 12 after the index date. Eyes were excluded if there was a treatment break of > 11 months at any point in the 24 months following the index injection. Only VA readings from accepted measurements were used (distance corrected, near corrected, or pinhole). To ensure comparable results, all VA measurements for an individual patient were required to use the same methodology; approximate Early Treatment Diabetic Retinopathy Study (ETDRS) letters were calculated using the formula ETDRS = 85 – (50 × logMAR).

Observation Period

Eyes were observed for 12 to 24 months following the index injection. Inclusive of all eyes, the observation period lasted from January 1, 2012, to April 30, 2017.

Cohorts

For data analysis, eyes were divided into 2 cohorts: year 1 cohort (eyes that were treated for ≥ 1 year) and year 2 cohort (eyes that were treated for 2 years). Each of these cohorts was further divided into 2 subcohorts based on whether 6 or fewer or more than 6 injections were administered per year (hereafter referred to as the ≤ 6 injections and > 6 injections subcohorts, respectively).

Statistical Methods

Descriptive statistics were calculated for year 1 and year 2 cohorts to identify changes in injection frequency and ETDRS letters over time. Paired *t* tests were performed within cohorts to determine whether the changes in letters over time were significant. Independent *t* tests assuming unequal variance were used to determine whether differences in changes in ETDRS letters between cohorts were significant. Calculations were performed using Microsoft Excel, and *P* values < .05 were considered statistically significant.

Results

Patients

A total of 155 240 eyes with DME were assessed for eligibility (Figure 1). Of these, 13 016 had their first anti-VEGF treatment between January 2012 and April 2015, and a VA reading on the date of the index injection. Following the exclusion of eyes without the required quarterly VA readings, sex identification, and those with treatment breaks longer than 11 months during follow-up, 3028 (≤ 6 injections, n = 1303; > 6 injections, n = 1725) eyes were included in the year 1 cohort and 1292 (≤ 6 injections, n = 594; > 6 injections, n = 698) eyes were included in the year 2 cohort. Overall, 45% (n = 1354) of eyes in the year 1 cohort qualified for inclusion in the year 2 cohort; however, 28% (n = 837) did not have any follow-up visits during year 2.

In the year 1 study cohort, the mean patient age was 62.2 years and 45.7% of patients were female (Table S1). Mean baseline VA was 55.5 letters and more than three-quarters of patients had a VA of 50 letters or more at baseline. Demographic and baseline characteristics were similar in the ≤ 6 injections and > 6 injections subcohorts.

Year 1 Outcomes

For eyes that were treated for 1 or more years, eyes in the ≤ 6 injections subcohort received a mean total of 4.0 injections (range, 1-6 injections), whereas eyes in the > 6 injections subcohort received a mean total of 9.1 injections (range, 7-14 injections; Table 1) at year 1. The mean number of injections was highest during the first quarter of year 1 (≤ 6 injections: 2.0 injections; > 6 injections: 3.0 injections), decreased during the second quarter (≤ 6 injections: 0.7 injections; > 6 injections: 2.2 injections), and then remained relatively constant in the third (≤ 6 injections: 0.6 injections; > 6 injections: 2.0 injections) and fourth quarters (≤ 6 injections: 0.7 injections; > 6 injections: 2.0 injections).

The greatest increase in mean VA occurred during the first quarter of year 1 for both subcohorts (≤ 6 injections: +5.2 letters; > 6 injections: +5.6 letters; Figure 2). VA increased slightly for each quarter of year 1 in the > 6 injections subcohort. In the ≤ 6 injections subcohort, VA remained relatively stable in the second and third quarters of year 1, and then slightly decreased in the fourth quarter. At the end of year 1, the mean change from baseline VA was significantly greater in

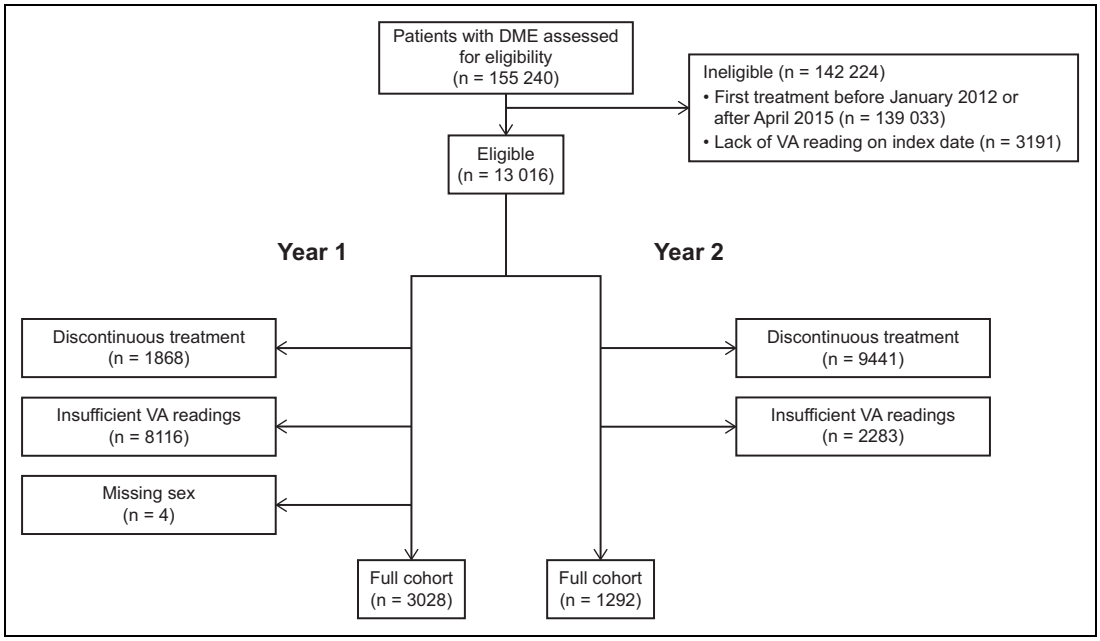

Figure 1. Patient disposition. DME indicates diabetic macular edema; VA, visual acuity.

Table 1. Number of Antivascular Endothelial Growth Factor Injections in Eyes by Quarter in the Year 1 Cohort.

	No. of injections				
Cohort	Q1	Q2	Q3	Q4	Year 1
All eyes (n = 3028)					
Mean injections	2.6	1.6	1.4	1.4	6.9
Range	1-5	0-4	0-4	0-6	1-14
≤ 6 injections (n = 1303)					
Mean injections	2.0	0.7	0.6	0.7	4.0
Range	1-4	0-3	0-3	0-3	1-6
> 6 injections (n = 1725)					
Mean injections	3.0	2.2	2.0	2.0	9.1
Range	1-5	0-4	0-4	0-6	7-14

Abbreviation: Q, quarter.

the > 6 injections subcohort than in the ≤ 6 injections subcohort (+8.0 vs +3.7 letters, respectively; $P < .001$). The differences in mean VA between the 2 subcohorts were statistically significant at Q3 and Q4 in year 1 ($P < .05$).

Year 2 Outcomes

Of the eyes in the year 2 cohort, 27.4% (354 of 1292) received ≤ 6 injections in year 1; of these, 65.0% (230 of 354) also received ≤ 6 injections in year 2. Eyes in this subcohort received a mean total of 4.6 (range, 2-6) injections in year 1 and 4.3 (range, 2-6) injections in year 2. For the subcohort of eyes administered ≤ 6 injections in year 1 and > 6 injections in year 2 (n = 124), the mean total number of injections received was 4.9 (range, 2-6) in year 1 and 8.2 (range, 7-12) in year 2. Of the eyes in the year 2 cohort, 72.6% (938 of 1292) received > 6 injections in year 1; of these, 38.8% (364 of 938) received ≤ 6 injections in year 2. In this subcohort, the mean total number of injections received in the first and second years was 8.8 (range, 7-13) and 4.7 (range, 2-6), respectively. For the subcohort that received > 6 injections in both year 1 and year 2 (n = 574), the mean total number of injections received was 9.7 (range, 7-13) in year 1 and 9.0 (range, 7-14) in year 2.

Overall, mean VA remained relatively constant from year 1 to year 2 in eyes that remained in the same injection subcohort for both years. Mean VA increased slightly from year 1 to year 2 in eyes that received ≤ 6 injections in year 1 and > 6 injections in year 2. The change was not statistically different from that in eyes that received ≤ 6 injections in both years 1 and 2 (+0.8 vs –0.4 letters; $P = .31$; Figure 3). By contrast, eyes that received > 6 injections in year 1 but ≤ 6 injections in year 2 had a significantly greater loss in mean VA from year 1 to year 2 than those that received > 6 injections per year in both years 1 and 2 (–2.8 vs –0.5 letters; $P = .01$; Figure 3).

Annual Trend in Treatment Frequency

The mean number of anti-VEGF injections received during the first year of treatment remained relatively constant over calendar years 2012 to 2015, ranging from 6.7 to 7.0 injections (Table 2). During 2012 to 2015, slightly greater proportions of eyes received > 6 injections vs ≤ 6 injections during the first year of treatment (52%-59% vs 41%-48%, respectively).

Conclusions

A substantial proportion of patients with DME worldwide do not receive optimal treatment, despite evidence that frequent and consistent treatments are essential to attain optimal visual outcomes in clinical practice similar to that seen in randomized

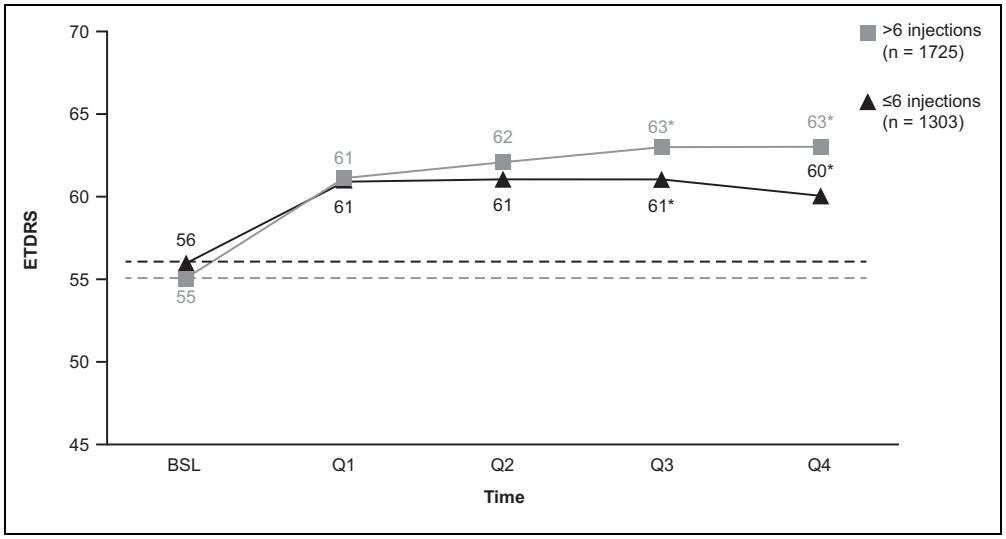

Figure 2. Mean visual acuity of eyes in the year 1 cohort that received ≤ 6 antivascular endothelial growth factor injections or > 6 injections during the first year of treatment. Dotted lines indicate baseline (BSL) visual acuity. ETDRS indicates Early Treatment Diabetic Retinopathy Study letters; Q, quarter. *Statistical significance between the 2 cohorts ($P < .05$).

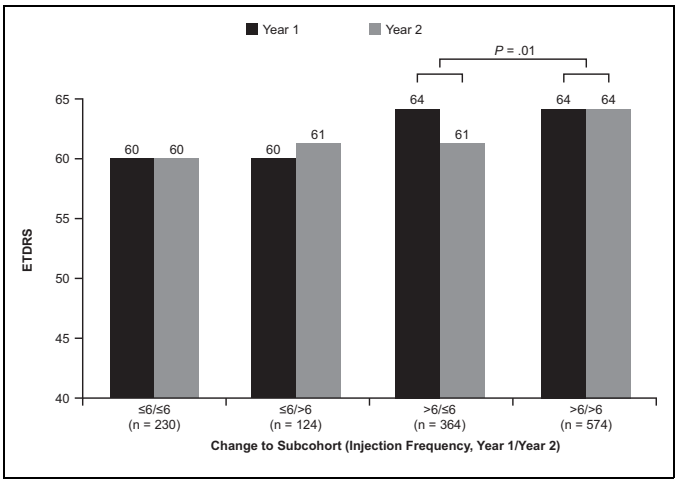

Figure 3. Mean visual acuity (Early Treatment Diabetic Retinopathy Study [ETDRS] letters) of eyes in year 1 vs year 2 stratified by injection frequency in year 1 and year 2.

Table 2. Mean Number of Injections in 2012-2015 and the Proportion of Eyes Administered ≤6 or >6 Injections During Year 1.

	Year			
	2012	2013	2014	2015
Mean injections/y	6.7	6.8	7.0	6.8
Injection subcohorts				
Eyes, n	143	594	1585	706
≤ 6 injections, %	43	48	41	43
> 6 injections, %	57	52	59	57

clinical trials.[12-19] Our analysis of electronic medical records captured in the Vestrum Health treatment and outcomes database further provides credence to these findings by first showing that only approximately half of the eyes with DME seen in clinical practice in the United States are receiving > 6 injections during the first year of follow-up. Second, although initial VA gains were similar for both subcohorts in the first quarter of treatment, eyes that received > 6 injections maintained their vision over time through the end of the first year, consistent with that seen in clinical trials. However, in eyes that received treatments less frequently, initial VA gains declined over time, resulting in suboptimal VA at the end of the year.

The difference in the patterns for visual change in the first year can be attributed to not only the total number of injections over the year but also their distribution over this time period. An average of 3 initial monthly injections followed by a mean of approximately 2 injections per quarter resulted in an approximate mean of 9 injections in the first year for eyes in the > 6 injections subcohort, indicating a consistent and frequent dosing schedule. Eyes in the ≤ 6 injections subcohort received an average of 2 initial doses followed by a mean of < 1 injection in each quarter, resulting in only 4 injections over the first year, which may explain the decline in VA gains at the end of the first year observed in this subcohort.

Prior studies using the Vestrum Health database have reported that less-frequent treatments in clinical practice result in modest visual gains; however, these evaluations were limited to certain time points and not over time based on injection categories as performed in this study.[20,21]

VA changes in the second year of follow-up were minimal across all subcohorts, except for eyes that were treated with > 6 injections in the first year and subsequently treated with a lesser frequency in the second year (loss of 2.8 letters). Even eyes that received ≤ 6 injections in the first year who went on to receive > 6 injections during the second year, on average, gained < 1

letter in the second year. This suggests that the first year of treatment following the diagnosis of DME is important to achieve optimal visual gains, which can be maintained with consistent and frequent dosing during the additional follow-up period.

It is generally believed that eyes with good vision might not require frequent treatments and, hence, we would expect that the subcohort of eyes receiving ≤ 6 injections would have better vision at the start of treatment. In fact, both subcohorts presented with similar starting VAs, indicating other potential clinical factors may have influenced treatment schedules.

Furthermore, our study showed that there was a lack of change over time in treatment frequency during the study period (2012-2015), suggesting that retina specialists have not yet adopted treatment practices for DME that more closely reflect protocols from randomized controlled trials. This contrasts with a nominal steady increase in treatment frequency reported in a recent study of patients with neovascular age-related macular degeneration.[22] Patient noncompliance may, at least in part, explain the lack of more frequent treatment in DME, because 28% of patients in the year 1 cohort in our study did not have any follow-up visits with their retina specialist in year 2. Similarly, Best et al[12] reported that approximately 25% of their patients were lost to follow-up at 1 year.

Our study is one of the largest analyses of treatment patterns and visual outcomes in eyes with DME in routine clinical practice. However, our real-world study was limited by its retrospective nature, lack of standardized protocols for clinical measurements and treatments, and the potential for missing data. Furthermore, because we analyzed aggregate data from a health care database rather than individual patient data, it was not possible to identify specific factors that may have been associated with treatment outcomes. Additionally, treatment of some patients may have been biased, owing to limited therapeutic potential (perceived or actual). For example, some physicians may treat patients with very poor vision less frequently because of their perceived limited therapeutic potential. Conversely, some patients presenting with good vision may not be treated as aggressively as those with worse vision because of the perceived ceiling effect limiting the amount of possible improvement. Although these situations are difficult to control, they are representative of the complex variables encountered in routine clinical practice. Finally, we excluded eyes for which we did not have complete vision data, limiting our sample population.

Nevertheless, analysis of health care databases may help retina specialists optimize treatment patterns and outcomes in patients with DME who are treated with anti-VEGF injections. Our results provide additional support for the finding that injection frequency could be a key factor to achieving and sustaining improvements in vision in clinical practice. Further research is needed to elucidate the underlying barriers that lead to undertreatment, and effective strategies are needed to overcome these barriers to optimize treatment frequencies and outcomes in patients with DME.

Authors' Note

Namrata Saroj is now affiliated with All Eyes Consulting, LLC, New York, NY, USA. The results of this study were presented at the 2018 American Society of Retina Specialists Annual Meeting, July 20 to 25, 2018, in Vancouver, British Columbia, Canada.

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Qualified researchers may request access to study documents (including the clinical study report, study protocol with any amendments, blank case report form, and statistical analysis plan) that support the methods and findings reported in this article. Individual anonymized participant data will be considered for sharing once the indication has been approved by a regulatory body, if there is legal authority to share the data and there is not a reasonable likelihood of participant reidentification. Submit requests to https://vivli.org/.

Ethical Approval

Deidentified electronic medical records of patients with DME in the Vestrum Health treatment and outcomes database constitute a limited data set in which all patient identifiers have been completely removed and site and clinician data pseudoanonymized. On this basis, formal ethics approval was not required and thus not obtained.

Statement of Informed Consent

For the same reasons as given for Ethical Approval, informed consent was not required, and informed consent approval was not obtained from patients.

Declaration of Conflicting Interests

The author(s) declare the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: John D. Pitcher has served as a consultant for Allergan, Genentech, Novartis, Regeneron Pharmaceuticals, Inc, and REGENXBIO and as a speaker for Genentech, Novartis, and Regeneron Pharmaceuticals, Inc. He has also received research support from Alcon. Andrew A. Moshfeghi has served as a consultant for Allegro, Allergan, Alimera, Graybug, Regeneron Pharmaceuticals, Inc, Genentech, Clearside, Bausch, EyePoint, and Novartis and as a speaker for Allergan. He has also received research support from Allegro, Novartis, Genentech, and Regeneron Pharmaceuticals, Inc, and holds equity interest in Pr3vent, OptiSTENT, and Visunex. Genevieve Lucas was a salaried employee of Vestrum Health at the time these analyses were undertaken. Nick Boucher is a salaried employee of Vestrum Health. Hadi Moini is a salaried employee of Regeneron Pharmaceuticals, Inc. Namrata Saroj was a salaried employee of Regeneron Pharmaceuticals, Inc at the time these analyses were undertaken. Dr Saroj also serves as a consultant for Amgen, Allegro, Apellis, RegenXBio, iRenix, and SamaCare and is an equity owner in Allegro, Pr3vent, iRenix, Retina Technologies, and SamaCare.

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participated in the design and conduct of the study, analysis of the data, and preparation of the manuscript.

Supplemental Material

Supplemental material is available online for this article.

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