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TREATMENT PATTERNS AND 2-YEAR VISION OUTCOMES WITH BEVACIZUMAB IN DIABETIC MACULAR EDEMA

An Analysis From a Large U.S. Integrated Health Care System

DONALD S. FONG, MD,* TIFFANY Q. LUONG, MPH,† RICHARD CONTRERAS, MS,† JENNIFER J. JIMENEZ, MA,† PETER H. CUSTIS, MD,‡ VAISHALI PATEL, PharmD, MS,§ JOANNA H. CAMPBELL, PhD§

Purpose: To assess health care utilization and vision outcomes over 2 years in patients receiving bevacizumab treatment in clinical practice for diabetic macular edema.

Methods: Patients with newly diagnosed diabetic macular edema who received an intravitreal bevacizumab injection within 12 months of initial diagnosis were identified from Kaiser Permanente's 350,000 patients with diabetes mellitus treated between 2008 and 2013. Snellen best-corrected visual acuity (BCVA), number of intravitreal injections, and patient characteristics were abstracted from the electronic record. The main outcome measure was change in BCVA.

Results: Three hundred and nine patients met the inclusion criteria and had 2 years of follow-up after their first bevacizumab injection. These patients had a mean of 3.1 injections (range, 1–17) during the 2-year follow-up. Mean BCVA improvement was 5.4 letters at 12 months and 5.3 letters at 24 months. Only 29.8% of patients demonstrated ≥3 lines of vision improvement from baseline, whereas 12.3% had ≥3 lines of vision loss from baseline at 24 months.

Conclusion: This is the largest U.S. clinical practice–based study of bevacizumab use in diabetic macular edema. Consistent with national studies, the frequency of injection was low. Average BCVA improvement was lower than in anti–vascular endothelial growth factor trials. Significant BCVA improvement was achieved in approximately 30% of patients with newly diagnosed diabetic macular edema.

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Real-world assessment revealed lower visual acuity gains and frequency of intravitreal bevacizumab injections in patients with diabetic macular edema compared with clinical trial reports. Increasing the number of anti–vascular endothelial growth factor injections or use of treatments with longer durations of action may improve vision in patients with diabetic macular edema.

In the United States, an estimated 29 million people are affected with diabetes[1]; within this population, there are an estimated 7.7 million individuals with diabetic retinopathy and 0.8 million individuals older than 40 years with diabetic macular edema (DME).[2,3] Patients with DME have significantly more comorbidities compared with those with diabetes with no DME and, consequently, have a significantly higher rate of health care resource utilization, highlighting the high burden of disease placed on this patient population.[4]

Landmark clinical trials in DME have demonstrated pronounced improvements in visual acuity with the anti–vascular endothelial growth factor (VEGF) agents ranibizumab, aflibercept, and off-label bevacizumab, alone or in combination with laser photocoagulation, compared with laser therapy alone.[5–9] In the pivotal trials, including RISE/RIDE, RESOLVE, PROTOCOL I, and BOLT, patients with DME were monitored and received monthly or near monthly intravitreal treatment during the first 12 months. Analyses of anti-VEGF treatment patterns in the clinical practice setting suggest that injection frequency and use of DME monitoring tools, such as diagnostic imaging, are much

lower than in clinical trials. Compared with almost monthly (9–12) anti-VEGF injections administered to patients in clinical trials, recent analyses of U.S. claims data reveal that the mean number of intravitreal bevacizumab injections received by patients with DME over the first 12 months of treatment is between 2 and 4.[10,11] An analysis of 1-year visual acuity outcomes from electronic medical records (EMRs) suggests that infrequent dosing might compromise the extent of vision improvement gained with anti-VEGF therapy during the first 12 months of treatment.[12] Similarly, studies on anti-VEGF therapy in age-related macular degeneration point to less frequent anti-VEGF dosing and poorer visual acuity outcomes in the real-world setting compared with randomized controlled trials of fixed and as-needed dosage regimens.[13] The current study was conducted to characterize treatment patterns and vision outcomes over a 2-year period in real-world patients with newly diagnosed DME receiving treatment with intravitreal bevacizumab—the most widely used anti-VEGF agent in ophthalmology practice in the United States.

Methods

Study Design and Data Source

This was a retrospective, observational cohort study conducted by Kaiser Permanente Southern California, a prepaid health care provider for over 3 million patients. Enrolled patients are racially and ethnically diverse, and representative of the population of the state of California. Eye care is provided by 13 ophthalmology departments and 36 full-time retina specialists within the health care system. The Kaiser Permanente HealthConnect EMR data include longitudinal patient-level information on demographics, medical and medication histories, ambulatory care visits and inpatient admissions, associated clinical diagnoses, orders for laboratory tests, medications, and procedures, and laboratory and examination results. The EMR data contain outpatient and inpatient diagnoses and procedures, outpatient drug utilization, and dates of service. Medical, prescription, and patient encounter data are automatically linked to *International Classification of Diseases, Ninth Revision* (*ICD-9*) diagnosis codes. In compliance with the patient confidentiality requirements of the Health Insurance Portability and Accountability Act of 1996, all patient data used in this study were deidentified.

Patient Identification and Selection

Electronic medical records of 350,000 members of Kaiser Permanente Southern California health care system with diabetes mellitus treated between 2008 and 2013 were screened to identify patients who: 1) had a diagnosis of DME (*ICD-9* code 362.07 alone, or either code 362.53 or 362.83 plus a previous [within the last 12 months] diagnosis of type 2 diabetes [*ICD-9* code 250.xx]) in 2008 to 2013, verified using at least 2 in-person (outpatient, office visit, inpatient, emergency department visit, or hospital) encounters a minimum of 14 days apart; 2) did not have a concomitant diagnosis of age-related macular degeneration (*ICD-9* codes 362.42, 362.43, 362.52, or 362.50) or retinal vein occlusion (branch or central; *ICD-9* code 362.35 or 362.36); 3) received their first intravitreal anti-VEGF (bevacizumab, ranibizumab, or aflibercept) injection within 12 months of the initial diagnosis of DME and within the period 2008 to 2011; and 4) had continuous enrollment within the Kaiser Permanente Southern California system for at least 12 months before and at least 24 months after the initial (index) anti-VEGF injection. Records were further screened to identify patients who received bevacizumab only (no treatment with ranibizumab or aflibercept) during the study period and, in addition, received no intravitreal corticosteroid for the first 12 months of follow-up. Patients whose laterality of ocular disease or in whom index treatment could not be determined were excluded from the study.

Study Outcomes

Sociodemographic characteristics and clinical measures at the time of diagnosis and index bevacizumab

From the *Department of Ophthalmology, Southern California Permanente Medical Group, Baldwin Park, California; †Department of Research and Evaluation, Southern California Permanente Medical Group, Pasadena, California; ‡Department of Ophthalmology, Southern California Permanente Medical Group, San Diego, California; and §Allergan plc, Irvine, California.

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Reprint requests: Donald S. Fong, MD, Department of Ophthalmology, Kaiser Permanente Medical Center, 1011 Baldwin Park Boulevard, Baldwin Park, CA 91706; e-mail: Donald.S.Fong@kp.org

injection, including treatment history, Snellen best-corrected visual acuity (BCVA), and intraocular pressure, were collected for each patient. Previous treatment for DME was recorded, based on *Current Procedural Terminology* (*CPT*) or Healthcare Common Procedure Coding System (HCPCS) codes (laser photocoagulation [*CPT* codes 67210 or 67220], intravitreal triamcinolone [HCPCS codes J3301, J3302, or J3303 plus *CPT* code 67028, or HCPCS code J3300], and intravitreal dexamethasone [HCPCS code C9256 or J7312, or General Product Identifier code 863000100023]). In addition, cataract surgery before the index injection or during the study follow-up period was recorded. Anti-VEGF injections were identified from HCPCS codes for bevacizumab (J3490, J3590, J9035, Q2024, and C9257) accompanied by the *CPT* code for intravitreal injection (67028).

Health care resource utilization during the 24-month follow-up period after the index injection was assessed in terms of the number of ophthalmologist visits, the number of intravitreal anti-VEGF injections administered, and the number of optical coherence tomography (OCT; *CPT* codes 92135, 92133, or 92134) and fluorescein angiography (*CPT* code 92235) tests received. Snellen BCVA was recorded over the 24-month postindex period, and vision outcome was expressed in terms of the mean change from baseline in visual acuity (Early Treatment Diabetic Retinopathy Study [ETDRS] letter equivalents), and the proportion of eyes with no change (i.e., <5 (<1 line) ETDRS letter equivalents gain) and ≥ 5 (≥ 1 line), ≥ 10 (≥ 2 lines), and ≥ 15 (≥ 3 lines) ETDRS letter equivalents gain or loss. Visual acuity was measured with patients wearing their glasses or contact lenses, and pinhole acuity was also determined. Snellen BCVA values were converted to logarithm of the minimum angle of resolution and ETDRS letter scores (approxETDRS letters) using the published algorithm by Gregori et al.[14]

Data Analysis

Bevacizumab treatment and patient monitoring patterns, as well as visual outcomes, were assessed over 12-month and 24-month follow-up periods. Health care resource utilization and treatment outcomes were analyzed at the level of the eye; one eye from each patient was used for analysis, and if both eyes qualified, then the worse eye was considered the study eye. Analyses were performed with observed data only (i.e., no imputed data), and using an intention-to-treat approach where missing data were imputed using the last-observation-carried-forward (LOCF) method. Sensitivity analyses were conducted 1) in patients with baseline Snellen BCVA of 20/40 to 20/320, which is similar to the BCVA of patients enrolled in the pivotal RISE and RIDE clinical studies,[8] and 2) in patients with or without cataract surgery before or during the study.

Results

Study Population

A total of 6,740 patients were identified in the EMR database as having a diagnosis of DME between 2008 and 2013, of whom 5,904 patients had no concomitant diagnosis of age-related macular degeneration or retinal vein occlusion. Among this latter group, 1,173 patients initiated intravitreal anti-VEGF treatment within 12 months of the initial DME diagnosis and within the window from 2008 through 2011. A total of 309 patients met all the study eligibility criteria (Figure 1). Patient-level and eye-level demographic and clinical characteristics at the time of the index injection (baseline) are summarized in Table 1.

Health Care Utilization

Among the patient population (N = 309), 55.3% (n = 171) received unilateral bevacizumab treatment and 44.7% (n = 138) had bilateral treatment (defined as receiving bevacizumab injection in the fellow eye during the study period). The time from initial DME diagnosis to the index injection in the study eye was a mean (SD) 3.0 (3.2) months (range, 0–12). During the first 12-month follow-up period, study eyes received a mean (SD) 2.3 (1.6) bevacizumab injections (range, 1–11), inclusive of the index injection. A small proportion of eyes (9.7%; n = 30) received 3 injections within 90 days of initiating therapy, and the majority of eyes (96.7%; n = 299) received ≤ 6 bevacizumab injections over the first 12-month follow-up period. Only 1 eye (0.3%) received ≥ 10 injections over the first 12 months, a frequency approximating to monthly dosing (Figure 2). Patients had a mean (SD) 7.8 (4.5) ophthalmologist visits (range, 1–26) and a mean (SD) 2.0 (2.0) OCT and 0.7 (0.7) fluorescein angiography tests in the first 12-month follow-up period after the index injection.

During the second 12-month follow-up period (months 13–24), 29.8% (n = 92) of patients continued to receive intravitreal bevacizumab injections alone for treatment of DME. Study eyes from these patients (n = 92) received a mean (SD) 0.8 (1.7) injections (range, 0–9) during the 13- to 24-month follow-up period, and the patients had 5.0 (4.6) ophthalmologist visits (range, 0–21). Overall, during the entire 24-month

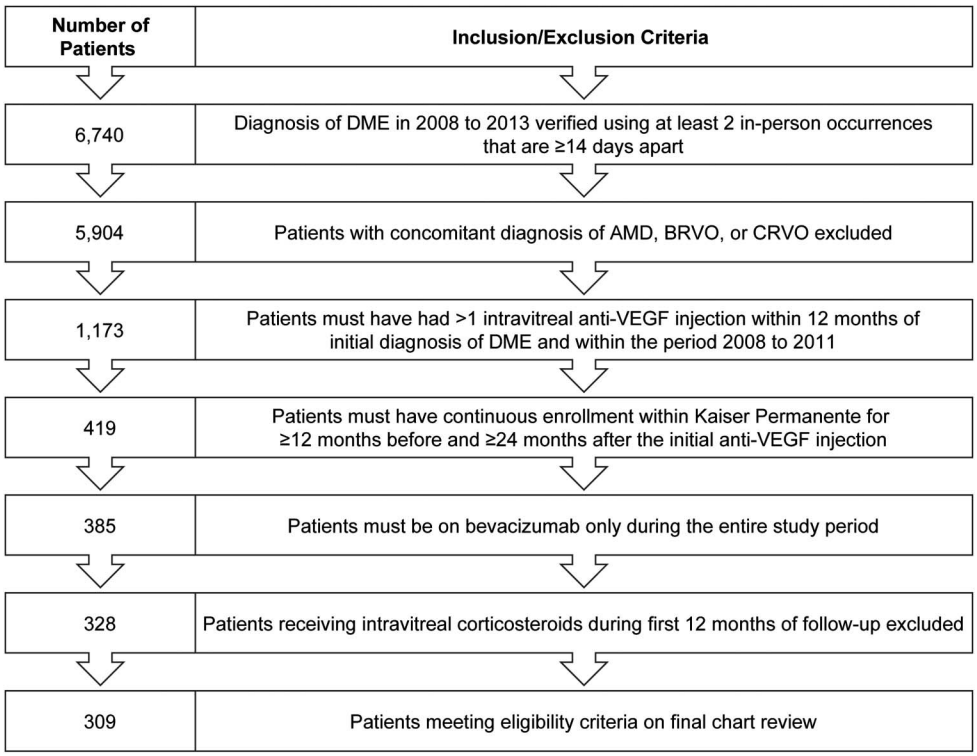

Fig. 1. Patient selection flowchart. In total, 309 patients were eligible to be enrolled in the study identified from Kaiser Permanente Southern California EMRs, and 1 eye of each patient (N = 309) was used for analysis of treatment outcomes. AMD, age-related macular degeneration; BRVO/CRVO, branch/central retinal vein occlusion.

follow-up period after the index injection, a mean (SD) 3.1 (2.8) bevacizumab injections (range, 1–17) were administered to study eyes (N = 309), patients had 12.8 (7.8) ophthalmologist visits (range, 1–43), and received 3.7 (3.3) OCT tests (range, 0–17).

The majority of study eyes received concomitant laser therapy during the follow-up period (191 [61.8%] over 12 months, 206 [66.7%] over 24 months). Use of intravitreal corticosteroids, which was restricted in accordance with the study design to the second 12-month follow-up period, was infrequent (21 [6.8%] study eyes).

Visual Acuity Outcomes

Among all study eyes evaluated (N = 309), BCVA improved by a mean (SD) 5.4 (21.3) ETDRS letters (LOCF analysis) at 12 months after index injection (Figure 3). During this time, the proportions of study eyes gaining ≥2 and ≥3 lines in vision were 36.7% (n = 101 of 275 eyes with approxETDRS score ≤75 letters at baseline) and 30.2% (n = 83 of 275 eyes with approxETDRS score ≤70 letters at baseline), respectively (Table 2). The proportions of study eyes losing ≥2 and ≥3 lines of vision (of 309 eyes with approxETDRS score ≤85 letters at baseline) were 11.7% (n = 36) and 10.4% (n = 32), respectively (LOCF analysis) (Table 2). Visual outcomes based on observed data were similar, with BCVA improvement of mean (SD) 4.7 (25.2) approxETDRS letters, 20.7% (n = 64) of eyes having better or equal to 20/40 vision, and 6.8% (n = 21) having worse than 20/200 vision at 12 months after the index injection.

Best-corrected visual acuity in the study eyes improved by a mean (SD) 5.3 (20.8) approxETDRS letters (LOCF analysis) at 24 months of follow-up after the index injection (Figure 3). The proportions of study eyes that gained ≥2 and ≥3 lines of vision reached 38.5% (n = 106) and 29.8% (n = 82), respectively, and the proportions of eyes that lost ≥2 and ≥3 lines of vision were 15.2% (n = 47) and 12.3% (n = 38), respectively, over the 24-month follow-up period after the index injection (LOCF analysis) (Table 2). Visual outcomes were slightly worse based on observed data, with BCVA improvement of mean (SD) 4.7 (23.2) approxETDRS letters and 16.2% (n = 50) of study eyes having better or equal to 20/40 vision; a similar proportion of eyes (6.1% [n = 19]) had worse than 20/200 vision at 24 months after the index injection.

Visual outcomes were generally lower in the subset of study eyes with baseline Snellen BCVA of 20/40 to 20/320 (n = 233), with fewer mean letters gained and lower proportions of eyes gaining ≥2 and ≥3 lines of vision at 12- and 24-month postindex than in the overall data set (Table 2). Among the study eyes categorized according to experience of cataract surgery, mean BCVA at 12 months was higher in surgery-

Table 1. Baseline Sociodemographic and Clinical Characteristics

Characteristic	N = 309
Age, years	
Mean (SD)	61.9 (11.4)
Range	23–88
Sex, n (%)	
Female	144 (46.6)
Male	165 (53.4)
Race, n (%)	
White	164 (53.1)
Black	49 (15.9)
Hispanic	44 (14.2)
Asian/Pacific Islander	31 (10.0)
Other	21 (6.8)
Visual acuity of study eye	
Snellen BCVA, median (range)	20/70 (20/20—hand motion)
20/40 or better, n (%)	65 (21.0)
Worse than 20/200, n (%)	42 (13.6)
Previous DME treatment in study eye, n (%)	
No treatment	202 (65.4)
Laser	95 (30.7)
Steroid	9 (2.9)
Laser and steroid	3 (1.0)
Medical history, n (%)	
Insulin use	172 (55.7)
Use of oral hypoglycemics	220 (71.2)
Use of statins	275 (89.0)
Use of antihypertensives	297 (96.1)
History of MI or stroke	66 (21.4)
Cataract diagnosis	239 (77.4)
Cataract surgery	85 (27.5)

MI, myocardial infarction.

naive eyes (mean 58.4 approxETDRS letters) than in those eyes that underwent surgery before or after the index injection (mean 55.9 and 52.0 approxETDRS letters, respectively); at 24 months post-index, BCVA was similar in the 3 groups (mean 56–58 approxETDRS letters) (Figure 4). Mean increases in BCVA from baseline to 24 months were markedly greater in eyes subjected to on-study (14 approxETDRS letters) compared with prestudy (6 approxETDRS letters) or no (1 approxETDRS letter) cataract surgery. The mean (SD) number of intravitreal bevacizumab injections administered over the 24-month follow-up period was similar among eyes that had no cataract surgery (3.4 [3.2]) and those that had prestudy (3.2 [2.9]) or on-study (2.9 [1.8]) cataract surgery.

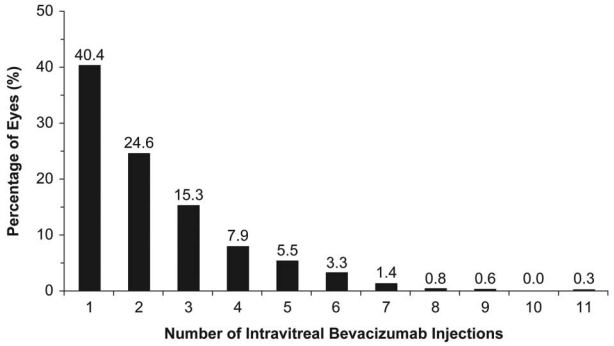

Fig. 2. Number of intravitreal bevacizumab injections administered over the first 12 months (N = 309).

Discussion

This large retrospective analysis uses EMRs from an integrated health care system database to assess health care utilization and vision outcomes over a 2-year period among a cohort of patients initiating bevacizumab treatment for DME between 2008 and 2011. Resource utilization data were captured over an extended time period (2008 through 2013), and confounding due to the use of rescue therapy was reduced by excluding patients who received intravitreal corticosteroids during the first year of follow-up. The study revealed that patients underwent relatively frequent ophthalmology visits (albeit not necessarily retina specialist visits) in the first year of treatment (mean 7.8) but received few (mean 2.3) intravitreal bevacizumab injections over this period. Less than 10% of patients received the 3 monthly loading doses routinely administered during the first 3 months of treatment in clinical trials, and less than 1% received near monthly (≥10) intravitreal injections during the first year of treatment. The frequency of ophthalmologist visits (mean 5.0) and bevacizumab injections (mean 0.8) decreased in the second year of follow-up. Overall, patients had a mean of 12.8 ophthalmology specialist visits, 3.1 intravitreal injections, and 3.7 OCT tests over the 24-month follow-up period after the index injection.

Health care utilization findings from this study are consistent with recent 1-year analyses of U.S. national administrative claims data, which indicated that patients initiating anti-VEGF therapy for DME between 2008 and 2010 received approximately 2 to 4 intravitreal injections during the first year.[10,11] This is in contrast to the pivotal clinical trials of anti-VEGF therapy in DME, where patients were monitored on a monthly basis (for at least the first 6 months) and received frequent intravitreal anti-VEGF injections (7–12) in the first 12 months of treatment.[5–9,15–17] The number of ophthalmology specialist visits undertaken during the first 12 months of follow-up was higher in this study (mean 7.8) than in the 2008 to 2010 claims data analyses (mean 4.4–5.3), whereas the number of OCT tests was marginally lower (mean 2.0 vs. 3.1–3.8, respectively).[10]

Table 2. Visual Outcomes in All Study Eyes and Study Eyes With Snellen BCVA 20/40 to 20/320 at the Index Injection (LOCF Analysis)

	All Study Eyes (N = 309)		Study Eyes With BCVA 20/40–20/320 (n = 233)	
	12-Month Visit	24-Month Visit	12-Month Visit	24-Month Visit
No. of approxETDRS letters gained after index injection				
Mean (SD)	5.4 (21.3)	5.3 (20.8)	2.9 (17.9)	2.6 (17.7)
Range	−76 to 80	−65 to 76	−65.1 to 45.2	−65.1 to 41.2
With Snellen BCVA ≥20/40, % (n)	39.2 (121)	33.3 (103)	37.3 (87)	30.0 (70)
With Snellen BCVA ≥20/200, % (n)	88.7 (274)	88.7 (274)	92.3 (215)	91.9 (214)
With Snellen BCVA <20/200*, % (n)	11.3 (35)	11.3 (35)	7.7 (18)	8.2 (19)
Improved ≥1 line in vision from index injection to follow-up visit†, % (n)	45.2 (138)	45.2 (138)	45.1 (105)	44.6 (104)
Improved ≥2 lines in vision from index injection to follow-up visit‡, % (n)	36.7 (101)	38.5 (106)	30.0 (70)	32.6 (76)
Improved ≥3 lines in vision from index injection to follow-up visit§, % (n)	30.2 (83)	29.8 (82)	22.3 (52)	22.3 (52)
Improved <1 line in vision from index injection to follow-up visit¶, % (n)	55.3 (171)	54.7 (169)	54.9 (128)	54.9 (128)
Lost ≥1 line in vision from index injection to follow-up visit**, % (n)	17.8 (55)	21.0 (65)	18.0 (42)	20.6 (48)
Lost ≥2 lines in vision from index injection to follow-up visit**, % (n)	11.7 (36)	15.2 (47)	10.7 (25)	13.7 (32)
Lost ≥3 lines in vision from index injection to follow-up visit**, % (n)	10.4 (32)	12.3 (38)	9.9 (23)	12.0 (28)

*Counting fingers, hand motion, light perception, and no light perception.
†Patients with approxETDRS score ≤80 at index injection (all patients, N = 305; Snellen BCVA 20/40–20/320, n = 233).
‡Patients with approxETDRS score ≤75 at index injection (all patients, N = 275; Snellen BCVA 20/40–20/320, n = 233).
§Patients with approxETDRS score ≤70 at index injection (all patients, N = 275; Snellen BCVA 20/40–20/320, n = 233).
¶Inclusive of lost vision (all patients, N = 309; Snellen BCVA 20/40–20/320, n = 233).
**Patients with approxETDRS score ≤85 at index injection (all patients, N = 309; Snellen BCVA 20/40–20/320, n = 233).

Although bevacizumab is not formulated specifically for use within the eye, the drug has been widely used off-label since 2006 for treatment of DME on account of its efficacy, availability, and considerably lower cost vis-à-vis ranibizumab and aflibercept.[18] The ability to substitute bevacizumab for ranibizumab or aflibercept offers scope for considerable reduction in treatment costs. Nevertheless, the evidence from clinical practice suggests that intravitreal injection frequency is similarly low in ranibizumab- and bevacizumab-treated patients.[19] Compared with clinical studies, monthly clinic visits may be difficult to maintain in real-world practice owing to patient-related factors such as poor motivation, transport issues, and treatment cost, as well as the presence of other diabetes-related comorbidities that also require regular monitoring and treatment. A recent retrospective analysis of Medicare claims data (2008–2012) indicated that the elderly DME population has a significantly higher prevalence of renal disease, cerebrovascular disease, congestive heart disease, peripheral vascular disease and myocardial infarction, and a significantly higher overall number of health care visits, than the non-DME diabetic population.[20] In addition, after an initial period of monthly intravitreal therapy, clinicians may choose a less frequent monitoring and treatment schedule based on assessment of patient response.[21] From an analysis of 1-year and 2-year clinical trials of ranibizumab in DME, an expert panel recommended initiating intravitreal anti-VEGF therapy on a monthly basis with monthly monitoring until BCVA stabilizes for a period of at least two consecutive visits or normal BCVA is achieved. The frequency of injections in the first year of treatment would optimally be similar to that in the RESTORE trial (i.e., five injections in the first 6 months and two in the second 6 months).[21] However, in our study, we found that only 9.7% of study eyes received three intravitreal bevacizumab injections within the first 3 months of treatment, suggesting a much lower frequency than the expert panel recommendation.

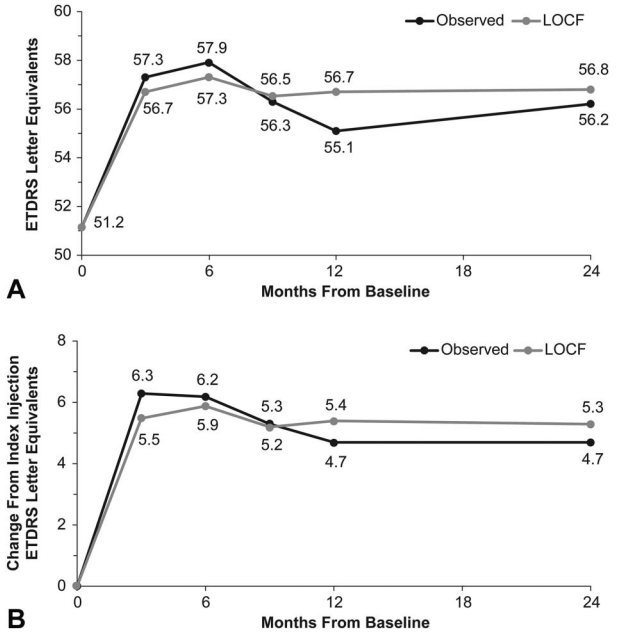

Fig. 3. A. Mean visual acuity and (**B**) mean change in visual acuity from baseline at follow-up visits (observed and LOCF analysis, N = 309).

Regardless of whether the ophthalmologist or patient chooses to extend the interval between successive intravitreal injections, clinical outcomes seem to be compromised by less frequent diagnostic monitoring and treatment. In this study, after 12 months of follow-up, BCVA had improved by a mean of 5.4 approxEDTRS letters, approximately 30% of study eyes had gained ≥3 lines of vision from baseline, and 20% of study eyes had BCVA better or equal to 20/40. Visual outcomes did not greatly change over the second year: after 24 months of follow-up, BCVA had improved by a mean of 5.3 approxEDTRS letters, approximately 30% of study eyes had gained ≥3 lines of vision, and 16% of study eyes had a BCVA of 20/40 or better. Moreover, sensitivity analysis findings

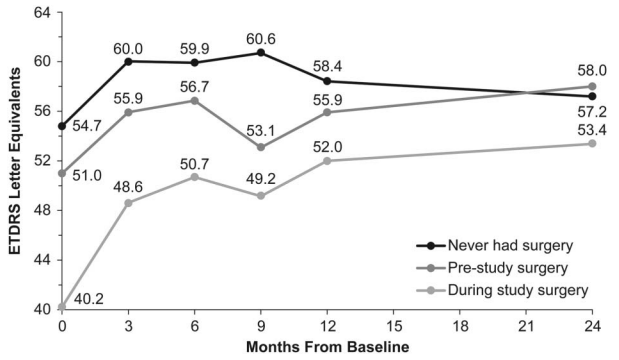

Fig. 4. Mean visual acuity at baseline and follow-up visits by cataract surgery experience (LOCF analysis; n = 163, never had surgery; n = 92, prestudy surgery; and n = 51, on-study surgery).

suggest that part of this overall vision gain was the result of correction of cataract, as indicated by the disproportionately large visual acuity improvement (mean increase 14 approxETDRS letters at 24 months) in those study eyes (16% of the total) that underwent on-study cataract surgery. Among the subset of eyes with baseline Snellen BCVA of 20/40 to 20/320, which approximates to the level of baseline BCVA impairment of patients enrolled in the Phase III RISE and RIDE clinical trials,[8] visual acuity gains were even more modest: after 24 months of follow-up, BCVA had improved by a mean of 2.6 approxEDTRS letters, and approximately 20% of study eyes had gained ≥3 lines of vision. In comparison, in the RISE and RIDE clinical trials of ranibizumab in DME, in which patients underwent monthly monitoring and received on average 11 intravitreal injections during the first year of treatment, BCVA improved by a mean of 11.9 and 12.0 ETDRS letters, respectively, and 39% and 46% of study eyes, respectively, demonstrated a ≥15-letter BCVA gain after 24 months of follow-up.[8] In other Phase III clinical trials, including RESOLVE, PROTOCOL I, BOLT, VISTA, and VIVID, BCVA improvements of approximately 8 to 12 ETDRS letters and BCVA response rates (≥10-letter gain) of 30% to 60% were achieved at 12 months after administration of approximately 9 to 12 intravitreal anti-VEGF injections.[5–7,9] Conversely, fewer than 5% of eyes were reported as losing ≥10 or ≥15 letters of vision in the pivotal Phase III studies, a figure considerably lower than the corresponding proportions (11.7% and 10.4%, respectively, at 12 months) in our analysis.

When evaluating visual outcomes, it is important to note that patients in clinical practice tend to be more diverse demographically and clinically than the patient populations enrolled in randomized clinical trials. Nevertheless, the results of this analysis of Kaiser Permanente data are consistent with those from a smaller retrospective 1-year study of EMR records (2007–2012) from the Geisinger health system in central and northeastern Pennsylvania.[12] In keeping with earlier analyses of national claims data,[10,11] the Geisinger study also showed that patients initiating anti-VEGF therapy for DME in clinical practice received infrequent monitoring and intravitreal injections (mean 2.7 over 12 months) and achieved modest vision outcomes at 12 months (mean improvement 5.4 ETDRS letters).[12]

Our analysis evaluated more recent, longer-term data derived from a larger EMR data set from an integrated health system, albeit one restricted to a single ethnically and socioeconomically diverse geographic region.

Other limitations of the study include the lack of information about DME status (duration of edema and presence of ischemia) and treatment to control the underlying diabetes. Use of *ICD-9* diagnostic code 362.53 (cystoid macular degeneration) in conjunction with *ICD-9* code 250.xx (diabetes) for identifying patients may have resulted in the inclusion of diabetic patients with cystoid macular edema resulting from uveitis or cataract surgery. The *ICD-9* diagnostic codes do not differentiate between center-involved and noncenter-involved DME, and hence, marked attrition is seen in the number of patients eligible for anti-VEGF therapy. Likewise, the inability to establish the subspecialty of the ophthalmology consultation at the "ophthalmologist visit" introduces possible confounding because of the inclusion of visits to nonretinal specialists. Moreover, when working with administrative claims data, errors may arise through coding inaccuracies. Finally, treatment practice in DME may have changed in recent years after publication of the randomized Phase III RIDE/RISE trials of monthly ranibizumab, the Protocol I trial of "as-needed" ranibizumab dosing, and the Protocol T comparative trial of bevacizumab, ranibizumab, and aflibercept in DME.[7,8,17] In Denmark, where anti-VEGF treatments (ranibizumab and aflibercept) are administered exclusively in the hospital setting, evidence from the national patient registry indicates that the mean number of anti-VEGF injections received by patients with DME during their first year of treatment rose marginally (from 5.3 to 5.9) between 2012 and 2014.[19] Likewise, contemporary studies of U.S. claims data suggest at best only a modest trend toward administering more frequent anti-VEGF injections in DME.[10]

Conclusion

Nonelderly patients with DME have a complex comorbidity profile and high rate of health care utilization, and understanding this burden is critical when managing this patient population.[4] Nevertheless, similar to previous analyses of national claims databases,[10,11] the results of this analysis show that utilization of anti-VEGF therapy in patients treated in the clinical setting is markedly less frequent than in landmark clinical trials. This study also documents less BCVA improvement and more vision loss than seen in landmark trials of anti-VEGF therapy. Increasing the number of injections or using treatments with longer durations of action may improve vision outcomes.

Key words: anti–vascular endothelial growth factor, bevacizumab, diabetic macular edema, electronic medical records, health care utilization, visual acuity.

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