Treatment Patterns of Anti-Vascular Endothelial Growth Factor and Laser Therapy Among Patients with Diabetic Macular Edema

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ABSTRACT

BACKGROUND: Diabetic macular edema (DME) is a form of diabetic retinopathy caused by continued leakage from retinal blood vessels. The use of anti-vascular endothelial growth factor (VEGF) injections has gained in popularity in the treatment of DME due to satisfactory efficacy, while laser photocoagulation is still the first-line therapy. Examining anti-VEGF treatment patterns may improve understanding of real-world medication-taking behaviors.

OBJECTIVES: To (a) compare demographic and clinical characteristics and treatment patterns of anti-VEGF (bevacizumab, ranibizumab, and pegaptanib) and laser therapies among DME patients and (b) determine predictors of switching and anti-VEGF therapy initiation.

METHODS: A retrospective cohort analysis was conducted with Texas Medicaid medical and prescription claims (January 1, 2008–December 31, 2012) for patients who were aged 18–63 years, continuously enrolled 1 year pre- and post-index, diagnosed with DME and treated with anti-VEGF or laser therapies. Treatment patterns included treatment frequency and switching between anti-VEGF and laser therapies. Logistic regression and multinomial analysis were used to determine factors associated with switching and initiation of anti-VEGF therapy, while controlling for demographic and clinical characteristics.

RESULTS: DME patients (N=2,201) were aged 54.7 (SD±7.9) years; 63.1% were female; 59.1% were Hispanic; and 10.3% were visually impaired. CCI mean score was 6.5 (SD±3.1), and patients were on 2.6 (SD±3.3) unique prescription medications. Anti-VEGF users had significantly ($P<0.0001$) fewer prescriptions compared with laser users (1.9 [SD±3.1] vs. 2.8 [SD±3.3], respectively). Laser was the most commonly used (84.9%) therapy from 2009 to 2011; however, anti-VEGF use increased from 11.7% in 2009 to 21.8% in 2011 ($P<0.0001$). Patients received 1.5 (SD±0.7) laser surgeries compared with 1.7 (SD±1.1) anti-VEGF injections per eye annually. Switching from laser to anti-VEGF injections was 9.7%, while switching from anti-VEGF injections to laser surgery was 42.2%. Patients who switched from anti-VEGF injections to laser surgery were more likely to be Hispanic (OR=1.415, 95% CI=1.037–1.930); male (OR=1.341, 95% CI=1.053–1.709); have fewer prescriptions (OR=0.944, 95% CI=0.905–0.985); and less likely to have no visual impairment (OR=0.641, 95% CI=0.449–0.915). Multinomial regression results showed anti-VEGF users were more likely to remain on the same therapy if they had more prescriptions (OR=1.094, 95% CI=1.029–1.172) or were female (OR=1.441, 95% CI=1.024–2.041). Anti-VEGF initiators had fewer prescriptions (OR=0.917, 95% CI=0.868–0.947) and initiated in 2011 vs. 2009 (OR=2.363, 95% CI=1.777–3.141).

CONCLUSIONS: Although anti-VEGF use is increasing, laser use is still more prevalent. Over 40% of patients who initiated on anti-VEGF injections switched to laser surgery. Additional research should be conducted to determine factors associated with this high rate of switching.

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What is already known about this subject

- Suboptimal outcomes from diabetic macular edema (DME) can lead to blindness, which is costly to the health care system. Laser surgery is the first-line treatment for DME.
- Ranibizumab was approved to treat age-related macular edema (AMD) in 2006 and DME in 2012.
- One study has shown an increase in use of anti-vascular endothelial growth factor (VEGF) among AMD patients. Anti-VEGF therapies have been shown by clinical trials to be effective in treating DME.

What this study adds

- This study is the first to use large claims data to determine the real-world treatment patterns of DME.
- Laser surgery was still more prevalent than anti-VEGF injections from 2009 to 2011 among patients with DME. The use of anti-VEGF injections increased from 2009 to 2011.
- Our study showed suboptimal use of anti-VEGF (<2 injections/year) and a high rate of switching from anti-VEGF therapy to laser therapy. Multinomial analysis found that female patients and patients with more prescriptions are more likely to stay on the same therapy.

Diabetic macular edema (DME) is a form of diabetic retinopathy caused by continued leakage from retinal blood vessels.¹ Laser photocoagulation and anti-vascular endothelial growth factor (VEGF) injections are common treatment choices for DME.² Laser (focal/grid) photocoagulation is the standard therapy for DME patients with visual impairment.³ Anti-VEGF treatment is a type of eye injection that causes VEGF inhabitation and prevents the formation of abnormal blood vessels and slows down the progression of DME. It is also used to treat age-related macular degeneration (AMD) and retinal vein occlusion.^{4,5} The use of anti-VEGF injections has gained in popularity due to satisfactory efficacy. Ranibizumab (Lucentis) was approved in August 2012 as an anti-VEGF therapy for DME. Clinical trials (RISE and RIDE) have shown advantages over laser therapy in preventing vision loss and improving visual acuity.⁶ However, the American Academy of Ophthalmology guidelines have recommended laser therapy as first-line treatment.³ The 2013 National Institute for Health and Clinical Excellence guidelines have

TABLE 1 CPT and HCPCS Codes for Anti-VEGF Injections, Laser Photocoagulation, and Steroids

Therapy	Code	Code Description	Effective Date	Payment (Unclassified)
Anti-VEGF	67028	Intravitreal injection	Still active	-
Bevacizumab	J3490	Unclassified drugs	July 1, 2006-December 31, 2009	\$1-\$100
	J3590	Unclassified biologics	July 1, 2006-December 31, 2009	\$1-\$100
	J9035	Cancer	Still active	-
Ranibizumab	J3490	Unclassified drugs	June 30, 2006-December 31, 2007	\$1,500-\$2,000
	J3590	Unclassified biologics	June 30, 2006-December 31, 2007	\$1,500-\$2,000
	J2778	Ranibizumab	Still active	-
Pegaptanib	J2503	Pegaptanib	Still active	-
Dexamethasone	J7312	Dexamethasone intravitreal implant	Still active	-
	C9256	Dexamethasone intravitreal implant	January 1, 2010-December 31, 2010	-
Fluocinolone acetonide	J7311	Fluocinolone acetonide intravitreal implant	Still active	-
Triamcinolone acetonide	J3301	Triamcinolone acetonide injection	Still active	-
Laser photocoagulation	67210	Destruction of localized lesion of retina (macular edema); photocoagulation	Still active	-
	67228	Treatment of extensive or progressive retinopathy	November 18, 2011-December 31, 2012	-
	67229	Treatment of extensive or progressive retinopathy	January 1, 2013- December 31, 2012	-

CPT = Current Procedural Terminology; HCPCS = Healthcare Procedure Coding System; VEGF = vascular endothelial growth factor.

recommended the use of ranibizumab as a treatment option for DME patients when central retinal thickness is greater than 400 micrometers.⁷

In a study that examined costs of DME among the elderly (treated and not treated), Shea et al. (2008) showed that laser therapy decreased from 43% in 2000 to 30% in 2004.⁸ Treatment patterns of anti-VEGF therapy among AMD patients have been evaluated in Medicare and commercial insurance populations.^{9,10} An increase in use of anti-VEGF therapy was detected, but monthly treatment was rare and discontinuation was high. Bevacizumab (Avastin) was the most commonly used anti-VEGF therapy among Medicare beneficiaries with AMD.⁹ Examining anti-VEGF treatment patterns may improve understanding of real-world medication-taking behaviors. Additionally, it will provide insight to ophthalmologists and other health care practitioners on anti-VEGF use, including regimen and treatment initiation and discontinuation. However, there is little information regarding how anti-VEGF therapy has been used for treating DME, especially for bevacizumab, which is used off label.^{3,11} A unique aspect of our study is the focus on the nonelderly Medicaid population. The objectives for this study were to (a) describe and compare demographic and clinical characteristics and treatment patterns (treatment frequency and switching) of anti-VEGF injections and laser photocoagulation among DME patients and (b) determine factors associated with switching and anti-VEGF therapy initiation.

Methods

Data Sources and Study Population

This is a retrospective secondary database study utilizing Texas Medicaid medical and prescription claims. Fee-for-service and

managed care claims data from January 1, 2008, to December 31, 2012, were obtained for all Texas Medicaid beneficiaries with a diagnosis of DME. *The International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes 362.07 (diabetic macular edema), 362.53 (cystoid macular degeneration), and 362.82 (retinal exudates and deposits) were used to identify DME patients from outpatient and inpatient claims. Newly treated patients (no treatment of anti-VEGF, laser, or steroids during the 1-year pre-index period) were selected from January 1, 2009, to December 31, 2011 (i.e., selection period). The earliest date within the selection period indicating anti-VEGF or laser treatment was selected as the index date. One-year pre-index and 1-year post-index periods were assigned to each patient. Patients continuously enrolled for 1-year pre- and post-index and those aged 18-63 years were included. The age limit of 63 years was used to avoid patients who were eligible for Medicaid/Medicare and because everyone was followed for 1 year. Patients were excluded if diagnosed with both AMD (ICD-9-CM code 362.52 [exudative senile macular degeneration], 362.42 [serous detachment of retinal pigment epithelium], and 362.43 [hemorrhagic detachment of retinal pigment epithelium]) and DME, treated with steroids, or identified as being treated with combination therapy. Because bevacizumab is also used to treat metastatic colorectal cancer, non-small cell lung cancer, metastatic renal cell carcinoma, and glioblastoma with progressive disease, patients with those conditions were also excluded.

Study Variables

Treatment patterns included treatment frequency and switching between anti-VEGF and laser treatment. Treatment frequency

FIGURE 1 Patient Selection Process

AMD = age-related macular degeneration; DME = diabetic macular edema; VEGF = vascular endothelial growth factor.

was defined as the number of anti-VEGF and laser therapies 1-year post-index. The Current Procedural Terminology (CPT) and Healthcare Common Procedure Coding System (HCPCS) codes used to identify treatments are listed in Table 1. Bevacizumab and ranibizumab were coded as unclassified drugs or biologics in an overlapped period. To separate them, a combination of code (J3490, J3590) and costs were used. Bevacizumab usually has a payment between \$1-\$100, and ranibizumab has a higher payment between \$1,500-\$2,000. Modifier codes for injections indicating right or left eye were used to determine whether patients were treated in 1 eye or 2 eyes. Switching between anti-VEGF therapy and laser therapy was defined as changing from the index treatment to the other therapy. The change must have occurred after 21 days from the last index treatment. If switching occurred prior to 21 days, it was identified as a combination therapy. Switching rate was calculated as the number of patients who switched from the index therapy divided by the total number of patients

who initiated that therapy. The rationale for using 21 days for combination therapy is that injections are typically given on a monthly basis, and any additional medications within 3 weeks were most likely used in combination with the index therapy. Independent variables included patient characteristics (age, gender, and race), Charlson Comorbidity Index score (CCI), number of unique medications, and visual impairment. CCI was calculated using the Deyo adaption.^{12,13} Number of unique medications was defined as the total number of different medications per patient at index date. To identify patients with visual impairments, ICD-9-CM codes 368.xx and 369.xx were used as well as patients who received Supplemental Security Income for blindness (category = 4).

Data Analysis

Descriptive statistics and t-test, Wilcoxon, and chi-square statistics were used to compare the demographic and clinical characteristics between anti-VEGF and laser users. Chi-square

TABLE 2 Comparison of Baseline Characteristics of Patients by Type of Index Treatment

Characteristics	Anti-VEGF Agents (n = 333)	Laser Photocoagulation (n = 1,868)	P Value
Age, mean [SD] ^a	54.5 [8.2]	54.7 [7.8]	0.676
Female, n (%) ^b	197 (59.2)	1,192 (63.8)	0.105
Race, n (%) ^b			
White	65 (19.5)	416 (22.3)	0.029 ^d
African American	40 (12.0)	295 (15.8)	
Hispanic	220 (66.1)	1,080 (57.8)	
Others	8 (2.4)	77 (4.1)	
CCI, mean [SD] ^a	6.6 [3.2]	6.5 [3.1]	0.834
Number of Rx, mean [SD] ^{a,c}	1.9 [3.1]	2.8 [3.3]	<0.0001 ^d
Visual impairment, n (%) ^b	43 (12.9)	183 (9.8)	0.084

^aT-test.^bChi-square test.^cNumber of unique medications at index date.^dP < 0.05.

CCI = Charlson Comorbidity Index; Rx = prescription SD = standard deviation; VEGF = vascular endothelial growth factor.

was used to compare the use of therapies from 2009 to 2011. Multinomial regression and logistic regression were used to predict switching and initiation of anti-VEGF therapy, while controlling for demographic and clinical characteristics. All analyses used an alpha value of 0.05.

Results

A final cohort of 2,201 patients was included in the study (Figure 1). Mean (standard deviation [SD]) age of patients was 54.7 (SD ± 7.9) years; 63.1% were female; 59.1% were Hispanic; and 10.3% were visually impaired. CCI mean score was 6.5 (SD ± 3.1). Patients were using 2.6 (SD ± 3.3) unique prescriptions. Patients treated with anti-VEGF therapy had fewer treatment prescriptions at index date compared with patients treated with laser therapy (1.9 [SD ± 3.1] vs. 2.8 [SD ± 3.3]). A significantly higher percentage ($P = 0.029$) of Hispanic patients (66.1% vs. 57.8%) were initiated on anti-VEGF therapy vs. laser therapy compared with Whites (19.5% vs. 22.3%) and African Americans (12.0% vs. 15.8%; Table 2). During the study period, laser therapy was the most common treatment (84.9%; Figure 2). From 2009 to 2011, however, the use of anti-VEGF therapy increased by 86.3% (11.7% to 21.8%), while laser therapy decreased 11.4% (88.3% to 78.2%, $P < 0.0001$; Table 3). The mean number of anti-VEGF injections during the 1-year post-index period was 2.4 (SD ± 1.8) per patient and 1.7 (SD ± 1.1) per eye. For patients treated with laser photocoagulation, the mean number of surgeries was 2.2 (SD ± 1.4) per patient and 1.5 (SD ± 0.7) per eye. Figure 3 shows the distribution of patients by number of anti-VEGF injections and laser surgeries. Among anti-VEGF users, 41.7% did not have a subsequent

FIGURE 2 Use of Anti-VEGF and Laser Therapy Among Patients with DME from 2009 to 2011

DME = diabetic macular edema; VEGF = vascular endothelial growth factor.

injection after the initial injection, whereas 38.8% did not have a subsequent laser surgery. Among anti-VEGF users and laser users, both had approximately two-thirds of patients (67.5% vs. 67.9%, respectively) with less than 3 treatments during the first-year follow-up.

Regarding anti-VEGF initiation, with a 1-unit increase in the number of unique prescriptions, the odds of initiating anti-VEGF therapy decreased by 9.3% (odds ratio [OR] = 0.907, 95% confidence interval [CI] = 0.868-0.947, $P < 0.0001$). Patients who started their treatment in 2011 were 2.4 times more likely to have been treated with anti-VEGF therapy instead of laser photocoagulation compared with patients treated in 2009 (OR = 2.363, 95% CI = 1.777-3.141, $P < 0.0001$).

The switching rate from laser photocoagulation to anti-VEGF therapy during the study period was 9.7%. Among patients who switched, about half (49.2%) switched after the first therapy. However, switching was more common from anti-VEGF injections to laser therapy. Among anti-VEGF users, 42.2% switched from anti-VEGF use to laser therapy during the first-year follow-up. Among patients who switched, over half switched after the first anti-VEGF treatment (55.8%). The logistic regression (Table 4) showed that for every 1-unit increase in number of unique prescriptions at index date, the odds of switching to laser decreased by 5.6% (OR = 0.944,

TABLE 3 Number and Incidence Rate of Treatment for Patients with DME from 2009 to 2011

Newly treated, n (%)	2009 (n = 675)	2010 (n = 779)	2011 (n = 747)	Total (n = 2,201)
Incidence ^a	N = 5,156	N = 5,735	N = 6,163	
Anti-VEGF agents	79 (11.7) 1.5%	91 (11.7) 1.6%	163 (21.8) 2.6%	333 (15.1)
Bevacizumab	64 (9.5) 1.2%	80 (10.3) 1.4%	139 (18.6) 2.3%	283 (12.9)
Ranibizumab	0 (0.0) 0%	2 (0.3) 0.03%	16 (2.1) 0.3%	18 (0.8)
Pegaptanib	15 (2.2) 0.1%	9 (1.2) 0.2%	8 (1.1) 0.1%	32 (1.5)
Laser photocoagulation	596 (88.3) 11.6%	688 (88.3) 12.0%	584 (78.2) 9.5%	1,868 (84.9)

Note: chi-square = 39.4; $P < 0.0001$.

^aIncidence of newly treated patients among DME patients.

DME = diabetic macular edema; VEGF = vascular endothelial growth factor.

95% CI = 0.905-0.985, $P = 0.0074$). Patients who had no visual impairment were 35.9% less likely than those with visual impairment to switch (OR = 0.641, 95% CI = 0.449-0.915, $P = 0.0142$). Male patients were 1.3 times more likely to switch compared with female patients (OR = 1.341, 95% CI = 1.053-1.709, $P = 0.0175$). Compared with White patients, Hispanic patients were 42% more likely to switch to a different therapy (OR = 1.415, 95% CI = 1.037-1.930, $P = 0.0441$). To further identify the switching behavior, a multinomial regression featuring a 3-level dependent variable was used (no switch, anti-VEGF to laser, and laser to anti-VEGF). Results showed that for anti-VEGF users, the odds of remaining on the same therapy was 1.1 times higher (OR = 1.094, 95% CI = 1.029-1.172, $P = 0.0052$) when there was a 1-unit increase in the number of unique prescriptions at index date. In addition, female anti-VEGF users were 1.4 times more likely to remain on the same therapy (OR = 1.441, 95% CI = 1.024-2.041, $P = 0.0362$). Because the majority of patients initiated with laser therapy, another post hoc logistic regression was conducted to examine switching among laser therapy starters. The results showed that among those patients who received laser surgery, patients who did not have visual impairment were 38.5% less likely to switch to anti-VEGF therapy (OR = 0.615, 95% CI = 0.390-0.968, $P = 0.0357$).

Discussion

Anti-VEGF therapy has been used increasingly to treat DME. According to our study, the use of anti-VEGF therapy increased by 86.3% from 2009 to 2011 (11.7% to 21.8%). Patients newly treated in 2011 were 2.4 times more likely to initiate anti-VEGF therapy compared with those in 2009. A similar trend of increasing anti-VEGF use among DME patients was also detected by Shea et al. (2000-2004).⁸ However, the most popu-

FIGURE 3 Distribution of Number of Anti-VEGF Injections/Laser Photocoagulation Surgeries Received After the Initial Injection (1-Year Post-Index)

VEGF = vascular endothelial growth factor.

lar treatment for DME is still laser photocoagulation (84.9%), which is expected since the guidelines have recommended it as the first-line therapy for DME.³ It is possible that patients were started with laser therapy first and that anti-VEGF therapies were used only on patients who had no improvement after laser photocoagulation.

The number of injections patients received each year was low. Based on our findings, DME patients treated with anti-VEGF injections have less than 2 injections per eye each year, which is much lower than the frequency indicated in clinical trials.⁶ In practice, the number of injections was dependent on the vision acuity improvement of the patients. So, it is hard to compare real-world treatment frequency with clinical trials. Our number is lower than other claims data studies, as well. The mean number of injections per year based on studies by Curtis et al. (2012) and Johnston et al. (2013) were 4.3 and 5.8, respectively.^{9,10} However, the populations for these 2 studies were focused on Medicare AMD patients, who usually require more injections than younger DME patients. In addition, the use of ranibizumab in Texas Medicaid requires prior

TABLE 4 Logistic Regression Results Examining Factors Related to Switching (N=2,201)

Covariates	Odds Ratio	95% CI		Wald X ²	P Value
Age	0.911	0.976	1.005	1.5787	0.2090
Male ^a	1.341	1.053	1.709	5.6430	0.0175 ^b
African Americans ^a	1.090	0.715	1.659	0.0363	0.8490
Hispanica	1.415	1.037	1.930	4.0510	0.0441 ^b
Others ^a	1.028	0.501	2.111	0.1115	0.7384
CCI	0.988	0.951	1.026	0.3987	0.5278
Number of Rx ^c	0.944	0.905	0.985	7.1821	0.0074 ^b
No visual impairment ^a	0.641	0.449	0.915	6.0090	0.0142 ^b

Note: Model Fit Statistics: Likelihood ratio = 30.5252, df=8, P=0.0002.

^aReference categories: females, Whites, visual impairment.

^bSignificant at P<0.05.

^cNumber of unique medications at index date.

CCI = Charlson Comorbidity Index; CI = confidence interval; Rx = prescription.

authorization, which has limited its use within Medicaid. After ranibizumab was approved to treat DME in August 2012, the use of anti-VEGF therapy was expected to increase. Further studies are needed to address the trend of anti-VEGF use after 2012.

Over 40% of patients switched from anti-VEGF to laser photocoagulation during the first year of therapy. The reason for this high switching rate is unclear. Anti-VEGF treatment consists of an injection in the eye that may be uncomfortable to patients, which may be one of the reasons that over half (55.8%) of the patients switched after the first anti-VEGF treatment. Besides the discomfort, patients also have perceived inconvenience of intravitreal injections.¹⁴ Another concern is safety. Ocular complications, including risk of retinal tear or detachment, uveitis (uvea inflammation), and vitreous hemorrhage, may occur among patients with anti-VEGF injections.¹⁵ Another risk is endophthalmitis (inflammation of the internal coats of the eye), which has occurred more prevalently with bevacizumab because of repackaging in compounding pharmacies.¹⁶ The main systematic safety problems of anti-VEGF injections are cardiovascular effects (i.e., hypertensive emergencies, hypertension, and arterial thromboembolic events), nonocular hemorrhaging, and gastrointestinal perforations.^{17,18}

Our study found that anti-VEGF users had fewer unique prescriptions at index date compared with patients treated with laser therapy (1.8 vs. 2.7); this may indicate that patients with potentially more medical issues were treated with laser treatment instead of anti-VEGF injections to avoid possible cardiovascular and hemorrhagic events.¹⁹ The relationship was also identified in the logistic regression, with a finding that patients with more unique prescriptions at index date were 9.3% less likely to initiate anti-VEGF therapy.

Texas Medicaid claims data are a rich and unique data source because of the large number of covered lives, diversity

of race/ethnicity (>50% Hispanic), and inclusion of individuals at risk for health disparities. Suboptimal outcomes from DME can lead to blindness, which is very costly to the health care system. To our knowledge, this is the first systematic analysis focusing on treatment patterns of DME. It is also the first study to use Medicaid claims data to examine anti-VEGF use. This study complements a Medicare claims database study on the use of anti-VEGF therapies among AMD patients between 2006 and 2008.⁹ In contrast, we examined a different population (DME patients, newly treated, and younger than aged 63 years) using Texas Medicaid data during a more recent period (2008-2012).

Limitations

This study has several limitations. First, claims data lack clinical detail on visual acuity outcomes. Although we identified patients who had visual impairment through ICD-9-CM codes and by using Supplemental Security disability status, some patients with less severe vision problems may not have been captured. The data also lacked detailed information such as the reason for visual impairment, so causality cannot be established. Second, we only collected data from 2008 to 2012. Although patients included in the study were treatment naïve 1 year prior to the index treatment, they may have received treatment in the prior years. Third, HCPCS codes for anti-VEGF injections may not have been coded correctly. Unclassified injection codes were used before specific codes were available. Although we identified bevacizumab and ranibizumab from other unclassified injections by the amount paid for each treatment, there could be misidentification. Fourth, although we included 333 anti-VEGF users in our study, ranibizumab users were a very small proportion (n=18), which limits comparisons among anti-VEGF agents. However, given the cost differences (during the study time frame) between ranibizumab (approximately \$1,200) and bevacizumab (approximately \$50) and the fact that ranibizumab required prior authorization, the small sample size of ranibizumab is not surprising.²⁰ Finally, the Texas Medicaid population provided unique insight into the Hispanic population with DME. However, this generalizability of the study may be limited, and results cannot be generalized to other populations or other state Medicaid programs.

Conclusions

A significant increase in the use of anti-VEGF injections occurred between 2009 and 2011. Although anti-VEGF treatment increased, only about one-third of patients had more than 3 injections in 1 year, and laser therapy is still the first line-treatment. Also, slightly over 40% of patients who initiated anti-VEGF treatment switched to laser therapy during the first year of treatment. Additional research should be conducted to determine factors associated with this high rate of switching.

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DISCLOSURES

Jiang, Barner, Park, and Ling declare no conflict of interest or financial interest in any therapy discussed in this article, including employment, honoraria, consultancies, expert testimony, patents, and royalties.

Study concept and design were primarily contributed by Jiang, along with Barner and assisted by Park and Ling. Data were collected by Jiang, Ling, Park, and Barner and interpreted by Jiang, Barner, Park, and Ling. The manuscript was primarily written and revised by Jiang, along with Barner, Park, and Ling.

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