OPEN

LONG-TERM OUTCOMES OF RANIBIZUMAB TREATMENT OF MYOPIC CHOROIDAL NEOVASCULARIZATION IN EAST-ASIAN PATIENTS FROM THE RADIANCE STUDY

NIKOLLE W. TAN, MD, FRCS,* KYOKO OHNO-MATSUI, MD, PHD,† HYOUNG J. KOH, MD,‡ YOSHIMI NAGAI, MD, PHD,§ MONTSE PEDROS, MD,¶ RITA L. FREITAS, MSC,** WAYNE MACFADDEN, MD,** TIMOTHY Y. LAI, MD, FRCOPHTH††

Purpose: To evaluate long-term efficacy and safety of ranibizumab for treatment of myopic choroidal neovascularization (mCNV) in clinical practice.

Methods: Noninterventional, retrospective cohort study of East-Asian patients previously treated with ranibizumab during the RADIANCE trial. Forty-one patients who completed the RADIANCE trial were followed-up for up to 48 months (post-RADIANCE observation period). Outcome measures were best-corrected visual acuity changes from baseline (assessed at RADIANCE trial initiation), mCNV recurrences, and ocular adverse events.

Results: Mean visual gain from baseline best-corrected visual acuity (56.5 ± 12.1 letters) (20/80) was significant at 12 months (+14.3 ± 11.4 letters, n = 40, $P < 0.0001$), 24 months (+10.4 ± 22.3 letters, n = 31, $P = 0.0143$), 30 months (+11.0 ± 22.4 letters, n = 29, $P = 0.0134$), 42 months (+12.9 ± 20.9 letters, n = 25, $P = 0.0051$), and 48 months (+16.3 ± 18.7, n = 16, $P = 0.0034$). Of the 16 patients who completed 48 months of follow-up, 63% gained ≥10 letters and 13% lost ≥10 letters. Over the post-RADIANCE observation period, 83% of patients required no further treatment for mCNV, 10% experienced mCNV recurrences, and 12% experienced a nonserious ocular adverse event. Patients who required additional treatment for mCNV received a mean of 5.0 (SD 5.9, range 1.0–18.0) ranibizumab injections.

Conclusion: Best-corrected visual acuity gained at the end of the RADIANCE trial was sustained over additional 36 months of follow-up. Few patients required further treatment and no new safety concerns were observed.

RETINA 38:2228–2238, 2018

Pathologic myopia (PM) is a leading cause of visual impairment with an estimated worldwide prevalence of 0.9% to 3.1%.[1] Asian populations have a higher prevalence of PM compared with white populations, with PM-related visual impairment reported to occur at a rate of 0.2% to 1.4% in Asian studies versus 0.1% to 0.5% in European studies.[1] The development of newly formed, pathologic blood vessels originating from the choroid, a process known as choroidal neovascularization (CNV), is one of the most common sight-threatening complications associated with PM.[2,3] Between 5% and 11% of patients with PM will develop myopic CNV (mCNV).[1] Without treatment, the prognosis for mCNV is poor, with over 90% of affected eyes likely to have a progressive and irreversible deterioration of vision leading to blindness within 10 years.[4–6]

Until 2013, verteporfin photodynamic therapy (vPDT) was the only Health Authority approved treatment for mCNV. Although studies showed that vPDT was more effective than placebo at stabilizing vision over 12 months, it did not improve visual acuity.[7–9] Since anti-vascular endothelial growth factor (anti-VEGF) therapy demonstrated superior efficacy over vPDT in terms of improvement in best-corrected visual acuity (BCVA),[10] it is now considered the first-line treatment for mCNV.[9,11,12] Ranibizumab, designed specifically for intraocular administration, was the first anti-VEGF therapy approved for the treatment of visual impairment due to mCNV in many countries worldwide.[13–16] The

efficacy and safety of ranibizumab was demonstrated in the Phase III RADIANCE and Phase II REPAIR clinical trials, where patients with mCNV treated with ranibizumab showed substantial vision gains.[16,17]

Although several studies have examined the long-term visual outcomes of mCNV treated with ranibizumab, most followed preestablished evaluation and treatment protocols.[18–26] This study provided an opportunity to understand how physicians were managing patients with mCNV previously treated with ranibizumab in clinical practice settings. Here, we assessed the real-world long-term effectiveness and safety of ranibizumab in East-Asian patients with visual impairment due to mCNV.

Methods

Study Design

This was a noninterventional, retrospective cohort study of patients with visual impairment due to mCNV in four East-Asian countries (Hong Kong, South Korea, Singapore, and Japan) who had participated in the RADIANCE trial, a 12-month randomized, prospective clinical trial comparing intravitreal ranibizumab treatment 0.5 mg (0.05 mL) (Lucentis; Novartis Pharma AG, Basel, Switzerland, and Genentech Inc, South San Francisco, CA) with vPDT.[16]

Three groups of patients participated in the clinical trial: Group I received ranibizumab on Day 1, Month 1 and thereafter as needed as per visual acuity stabilization criteria, Group II received ranibizumab on Day 1 and thereafter as per disease activity criteria, and Group III was treated with vPDT on Day 1 and disease activity was treated with vPDT and/or ranibizumab from Month 3 onward as per physician criteria. In Asia, a total of 87 patients were included.

The study was approved by local ethics committees in each country and performed in accordance with the ethical standards of the 1964 Declaration of Helsinki. In Japan, all patients provided informed consent, whereas informed consent waivers were obtained for Hong Kong, South Korea, and Singapore.

An overview of the study design is illustrated in Figure 1. Charts from routine clinical practice appointments of East-Asian patients who were previously treated with intravitreal ranibizumab during the RADIANCE trial were reviewed. Baseline was defined as the date of initiation onto the RADIANCE trial (between October 2010 and August 2012).[16]

The post-RADIANCE observation period was defined as the period starting from the first visit after completion of the RADIANCE trial until the last follow-up visit available in the patient's clinical chart (charts were reviewed between December 2014 and June 2015). During the post-RADIANCE observation period, patients were treated as per clinical practice, without any restriction on the drugs or treatment regimens used to treat mCNV. Follow-up visits during the post-RADIANCE observation period were at the discretion of the ophthalmologists involved. The time points for follow-up visits during this period were defined as the nearest visit within ±3 months to the time point assessed. Time points were assessed at 18, 24, 30, 36, 42, and 48 months from baseline.

Study Population and Sample Size

Patients were eligible for inclusion in the study if they completed the RADIANCE trial, had at least one subsequent follow-up visit, had available medical records, and in Japan had provided written informed consent. Patients were excluded from the study if they had participated in any interventional study after the RADIANCE final visit.

Patients were categorized into 2 post-RADIANCE treatment groups: Group A, those who required

From the *Eye Surgeons@ Novena, Mount Elizabeth Novena Specialist Centre, Singapore, Singapore; †Tokyo Medical and Dental University, Bunkyo-ku, Japan; ‡Department of Ophthalmology, The Institute of Vision Research, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea; §Department of Ophthalmology, Kansai Medical University, Hirakata, Japan; ¶RWE, IMS Health Spain, Barcelona, Spain; **Novartis Pharma AG, Basel, Switzerland; and ††Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong Eye Hospital, Kowloon, Hong Kong.

This study was funded by Novartis Pharma AG, Basel, Switzerland.

N. W. Tan received honoraria as a consultant from Bayer HealthCare and Novartis Pharma AG and lecture fees from Allergan, Bayer HealthCare, and Novartis Pharma AG. K. Ohno-Matsui received research funds from Novartis. H. J. Koh received lecture fees (honoraria) from Novartis Pharma AG and Bayer HealthCare. Y. Nagai received lecture fees (honoraria) from Novartis Pharma AG, Bayer HealthCare, and Santen Pharma Ltd. M. Pedros works as a consultant at IMS Health at the time of the study, which received funding from Novartis Pharma AG. R. L. Freitas worked as a consultant at Wellmera AG at the time of the study, which received funding from Novartis Pharma AG. W. Macfadden is a full time employee at Novartis Pharma AG. T. Y Lai received honoraria as a consultant from Allergan, Bayer, Genentech, and Novartis Pharma AG and lecture fees from Allergan, Bayer, and Novartis Pharma AG.

Under direction of the authors, Heidi Eriksen (GSM Safety Ltd) drafted the initial version of the manuscript. IMS Health provided overall study management, performed statistical analyses and verified accuracy of the data presented.

Reprint requests: Montse Pedros, MD, C/Provença 392, 3rd floor, 08025 Barcelona, Spain; e-mail: Montserrat.Pedros@quintilesims.com

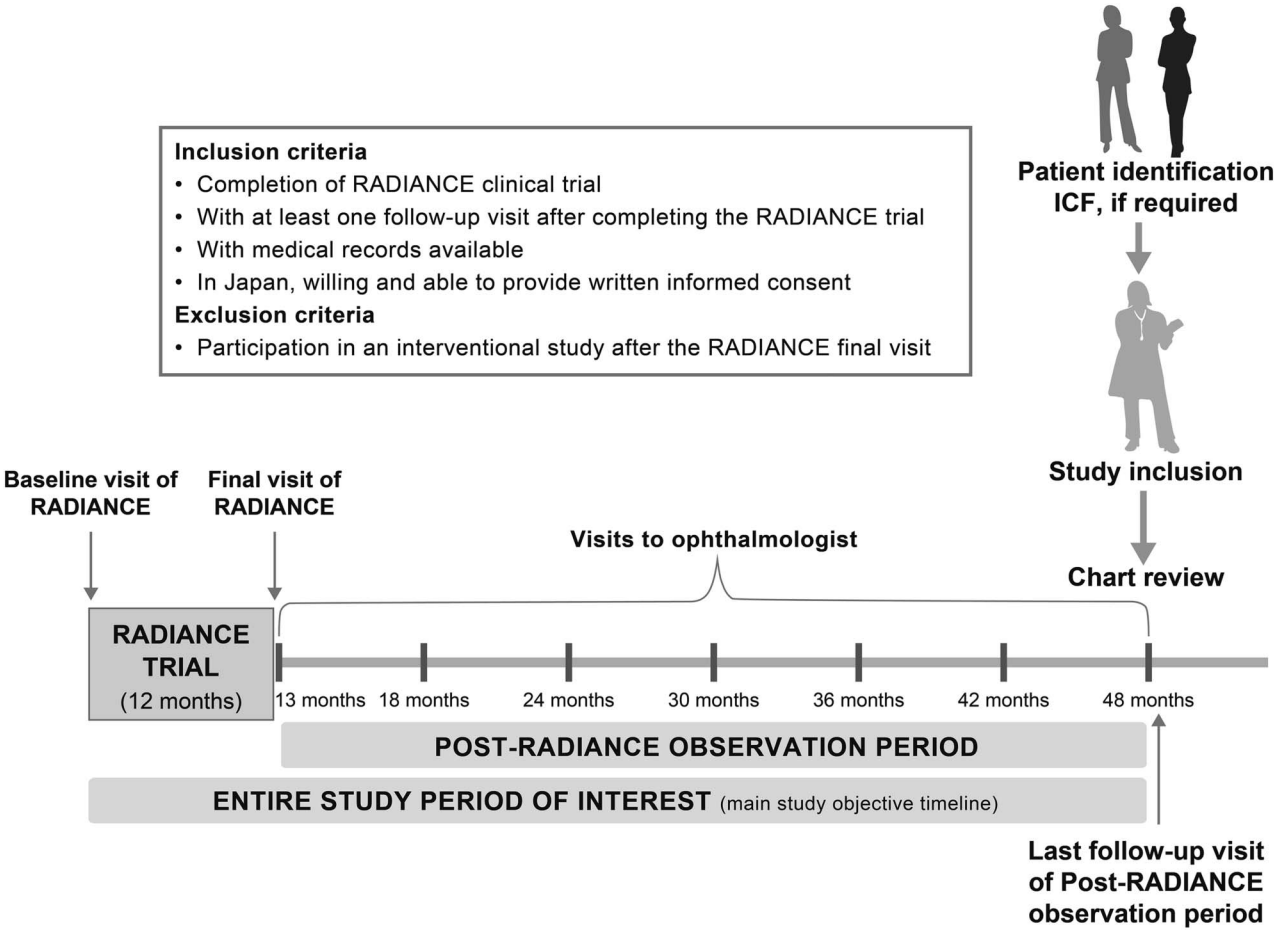

Fig. 1. Study design.

additional anti-VEGF during the post-RADIANCE observation period and Group B, those who required no further treatment.

The power and the effect size were estimated based on the improvement of BCVA. The RADIANCE trial described a SD of baseline BCVA (pooled sample) of 13.3 letters and the final sample size for this study was 41 patients. Based on this and assuming a paired *t*-test (one tailed), this study had 90% power at the 0.025 level of significance to detect a mean improvement in the BCVA score of 7.0 letters or greater.

Outcomes of Interest and Data Collection

The primary outcome of this study was to describe the long-term effectiveness of ranibizumab about the mean BCVA change from baseline to each follow-up visit during the post-RADIANCE observation period. Best-corrected visual acuity was reported in terms of Early Treatment Diabetic Retinopathy Study (ETDRS) letters. Secondary outcomes included the number, type and management of mCNV recurrences and identify predefined ocular adverse events (AEs) during the follow-up period.

For the purposes of this study, recurrences were defined as any sign of leakage or intraretinal or subretinal fluid as assessed by fluorescein angiography and/or optical coherence tomography after a period of 3 months without any sign of disease activity. Recurrences were classified as: 1) reactivation of a previously regressed CNV (i.e., lesion at the same location) or 2) newly formed CNV (i.e., lesion at different location than previously observed).

Demographic and clinical variables at baseline were retrieved from the original RADIANCE trial. Follow-up data were retrieved from patients' medical records for each of the visits to the ophthalmologist during the post-RADIANCE observation period. Data included BCVA, eye assessments, mCNV recurrences, therapeutic procedures and treatments due to mCNV, and ocular AEs. For the purposes of this study, any recorded Snellen fraction or decimal were converted to approximate ETDRS letters score to standardize measurement units.[27,28]

Statistical Analysis

Statistical analyses were conducted using SAS version 9.2 (SAS institute INC, Cary, NC). Patients were analyzed according to both the overall patient group and for each defined post-RADIANCE treatment group. Descriptive statistics for continuous variables were reported as mean, SD, and range and categorical variables were expressed as frequency and proportions with 95% confidence intervals.

The mean BCVA change from baseline visit to each follow-up visit during the post-RADIANCE observation period was reported and assessed using paired *t*-tests (one-tailed). *P*-values <0.05 were considered statistically significant. Best-corrected visual acuity was pooled to report proportions of patients in categories of change (gain or loss of ≥ 15 letters and gain or loss of ≥ 10 letters) with 95% confidence intervals.

The proportion of patients for each category of mCNV recurrence was reported as well as the total number, mean, and annualized rate of recurrences. Annualized rates were defined as the number of recurrence events divided by the total person-years. The proportion of patients receiving further treatments during the post-RADIANCE observation period was reported by type of drug administered. The mean and total number of injections administered to patients to treat mCNV during this period was determined. The proportion of patients who continued to receive solely ranibizumab treatment and the proportion who switched to other anti-VEGF agents during the post-RADIANCE observation period were reported. For each defined ocular AE reported, the proportion of patients by severity grade, its relationship to treatment, and serious adverse events were determined.

Results

Patient Demographics

Of the 267 patients who completed the 12-month follow-up in the RADIANCE trial, 87 patients were from the four participating countries in this study. A final of 41 patients were eligible for inclusion in this analysis (Figure 2): 7 (17.1%) from Hong Kong, 16 (39.0%) from Japan, 9 (22.0%) from South Korea, and 9 (22.0%) from Singapore. A total of 34 patients (82.9%) required no further treatment during the post-RADIANCE observation period (Group B). Baseline demographic and clinical characteristics of the included patients are described in Table 1. For the overall patient group, the mean age at baseline was 55.1 years (SD 13.5, range 24.0–87.0), and most patients were women (80.5%) and Japanese (39.0%), or Chinese (36.6%). The mCNV was observed in 27 left eyes (65.9%) and 14 right eyes (34.1%). Baseline mean BCVA in the study eye was 56.5 letters (SD 12.1, range 29.0–83.0) (20/80) for the overall patient group, 59.7 letters (SD 9.3, range 49.0–73.0) (20/63) for Group A, and 55.8 letters (SD 12.6, range 29.0–83.0) (20/80) for Group B. Overall, 27 patients (65.9%) presented with a subfoveal mCNV lesion. However, three patients (42.9%) from Group A and nine patients (26.3%) from Group B presented with juxtafoveal lesions. The mean total number of ranibizumab injections the patients received during the RADIANCE trial was 4.0 (SD 2.9, range 1.0–12.0). Three patients (42.9%) from Group A and six patients (17.6%) from Group B had been included in Group III of the RADIANCE trial (received vPDT at baseline then ranibizumab after Month 3).

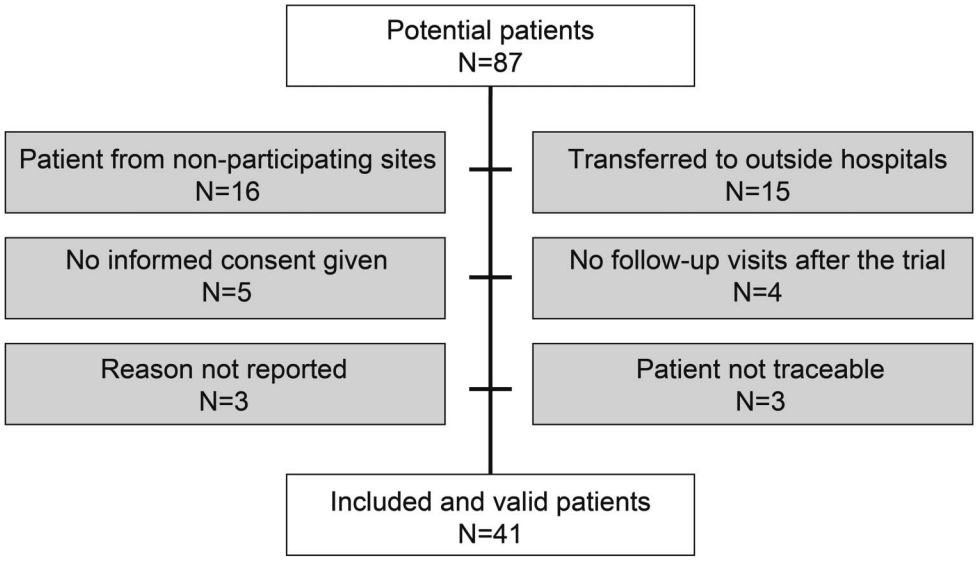

Fig. 2. Study participants.

Table 1. Baseline Demographic and Clinical Characteristics Stratified by Overall Patients and Post-RADIANCE Treatment Group

Variable	Overall (N = 41)	Group A: Required Additional Anti-VEGF (N = 7)	Group B: No Further Treatment (N = 34)
Mean (SD) age, years	55.1 (13.5)	55.3 (5.7)	55.0 (14.7)
Sex, n (%)			
Male	8 (19.5)	0	8 (23.5)
Female	33 (80.5)	7 (100)	26 (76.5)
Race, n (%)			
Asian	41 (100)	7 (100)	34 (100)
Ethnicity, n (%)			
Chinese	15 (36.6)	4 (57.1)	11 (32.4)
Japanese	16 (39.0)	3 (42.9)	13 (38.2)
Other	10 (24.4)	0	10 (29.4)
Eye with mCNV, n (%)			
Left eye	27 (65.9)	6 (85.7)	21 (61.8)
Right eye	14 (34.1)	1 (14.3)	13 (38.2)
Study eye characteristics			
Mean BCVA (SD), letters	56.5 (12.1)	59.7 (9.3)	55.8 (12.6)
Mean BCVA, Snellen; Mean CRT (SD), μm	20/80; 381.6 (102.5)	20/63; 379.0 (72.8)	20/80; 382.1 (108.6)
Mean IOP (SD), mmHg	14.5 (3.0)	15.1 (2.1)	14.4 (3.2)
Mean axial length (SD), mm	29.0 (1.8)	29.7 (2.0)	28.9 (1.7)
Mean refraction sphere (SD), D	10.6 (3.5)	11.8 (3.4)	10.4 (3.5)
mCNV location, n (%)			
Subfoveal	27 (65.9)	4 (57.1)	23 (67.6)
Juxtafoveal	12 (29.3)	3 (42.9)	9 (26.5)
Extrafoveal	1 (2.4)	0	1 (2.9)
Can not grade	1 (2.4)	0	1 (2.9)
RADIANCE trial randomization group, n (%)*			
Group I—ranibizumab 0.5 mg by stabilization	18 (43.9)	3 (42.9)	15 (44.1)
Group II—ranibizumab 0.5 mg by disease activity	14 (34.1)	1 (14.3)	13 (38.2)
Group III—vPDT with ranibizumab after Month 3	9 (22.0)	3 (42.9)	6 (17.6)
No. of ranibizumab injections during RADIANCE trial			
Mean (SD)	4.0 (2.9)	4.1 (2.9)	4.0 (2.9)
Median (range)	3.0 (1.0–12.0)	4.0 (1.0–9.0)	3.0 (1.0–12.0)

*During the RADIANCE trial, patients were divided into 3 randomized treatment groups as follows: Group I patients received ranibizumab 0.5 mg injections on Day 1 with further treatment determined by visual acuity stabilization. Group II patients received ranibizumab 0.5 mg injections on Day 1 with further treatment determined by disease activity. Group III patients received vPDT on Day 1 then after 3 months patients were treated either with ranibizumab, vPDT or both as guided by disease activity.

BCVA, best corrected visual acuity; CRT, central retinal thickness; IOP, intraocular pressure; mCNV, myopic choroidal neovascularization; EGF, vascular endothelial growth factor; vPDT, verteporfin photodynamic therapy.

The mean number of follow-up visits during the post-RADIANCE observation period was 8.4 (SD 6.5, range 1.0–28.0) for the overall patient group, 19.1 (SD 5.2, range 13.0–28.0) for patients in Group A, and 6.2 (SD 4.0, range 1.0–15.0) for patients in Group B. The mean follow-up during the post-RADIANCE observation period was 29.4 months (SD 11.1, range 2.8–42.8) for the overall patient group, 37.0 months (SD 3.9, range 30.8–42.6) for Group A, and 27.8 months (SD 11.5, range 2.8–42.8) for Group B.

Visual Acuity Assessment

Figure 3 describes the mean change in BCVA letters at each defined time point from baseline. In the overall patient group, the mean BCVA ± SD improved significantly from baseline by +14.3 ± 11.4 letters at 12 months (completion of the RADIANCE trial) (n = 40, $P < 0.0001$), +10.4 ± 22.3 letters at 24 months (n = 31, $P = 0.0143$), +11.0 ± 22.4 letters at 30 months (n = 29, $P = 0.0134$), +12.9 ± 20.9 letters at 42 months (n = 25, $P = 0.0051$), and +16.3 ± 18.7 letters at 48 months (n = 16, P =

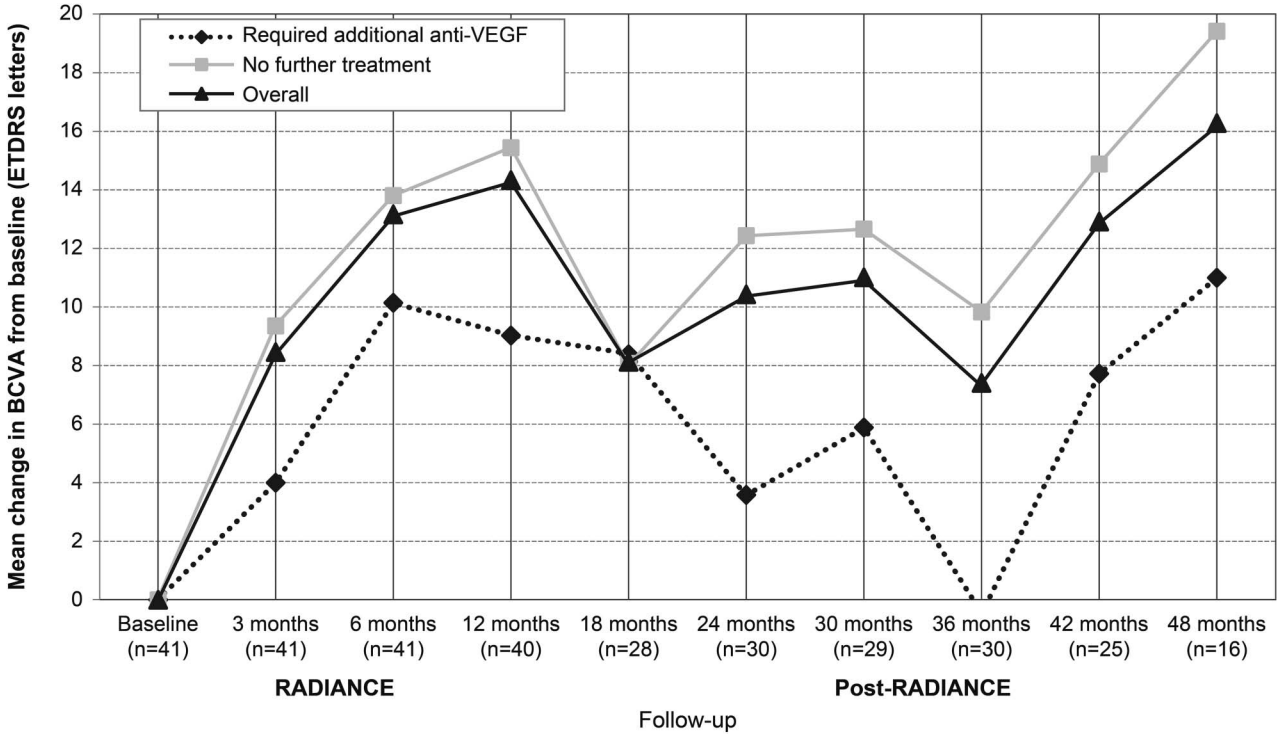

Fig. 3. Visual acuity outcomes. BCVA, best-corrected visual acuity; ETDRS, early treatment diabetic retinopathy study; VEGF, vascular endothelial growth factor.

0.0034). Sixteen patients overall (39.0%) and 10 patients (24.0%) from Group B completed 48 months (from baseline) of follow-up. The mean change in BCVA letters between Months 36 and 48 are presented in Figure 4. For patients in Group B, the mean BCVA ± SD improved significantly from baseline by +15.4 ± 12.2 letters at 12 months (<0.0001), +12.4 ± 22.5 letters at 24 months (P = 0.0126), +12.6 ± 22.9 letters at 30 months (P = 0.0173), 14.9 ± 22.9 letters at 42 months (P = 0.0134), and +19.4 ± 20.6 letters at 48 months (P = 0.0153). In Group A, the change in BCVA letters did not meet statistical significance at any point during the post-RADIANCE observation period.

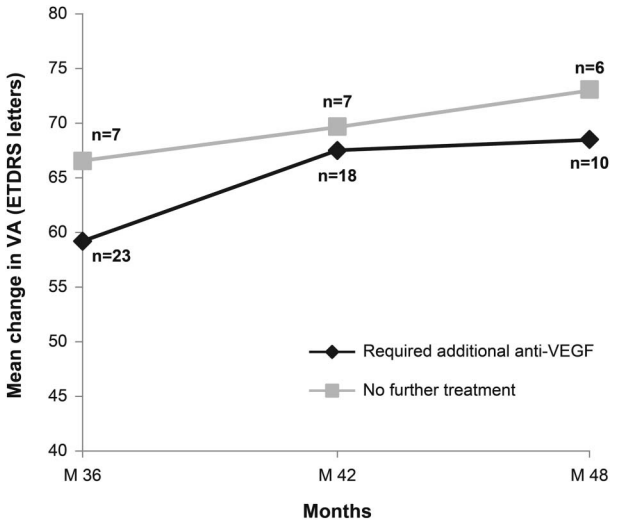

Fig. 4. Change in BCVA between Month 36 and Month 48 by group.

Figure 5 shows the proportion of patients in each categorized BCVA change group at different time points. At the end of the RADIANCE trial (12 months of follow-up), 40 patients overall had available data, of which 28 (70.0%) gained ≥10 letters, 19 (47.5%) gained ≥15 letters, and 2 (5.0%) lost ≥10 letters. After 24 months of follow-up, 31 patients overall had valid data of which, 18 (58.1%) gained ≥10 letters, 14 (45.2%) gained ≥15 letters, and 6 (19.4%) lost ≥10 letters. Of the 16 patients overall who reached 48 months of follow-up, 10 (62.5%) gained ≥10 letters, 9 (56.3%) gained ≥15 letters, and 2 (12.5%) lost ≥10 letters.

mCNV Recurrences

Frequency and type of mCNV recurrences during the post-RADIANCE observation period are described in Table 2. In the overall patient group, four patients (9.8%) had a total of six episodes of recurrences during this period; two patients (4.9%) had reactivations of a previously regressed mCNV and two patients (4.9%) presented with newly formed mCNV. Two patients (4.9%) had one episode of recurrence and two

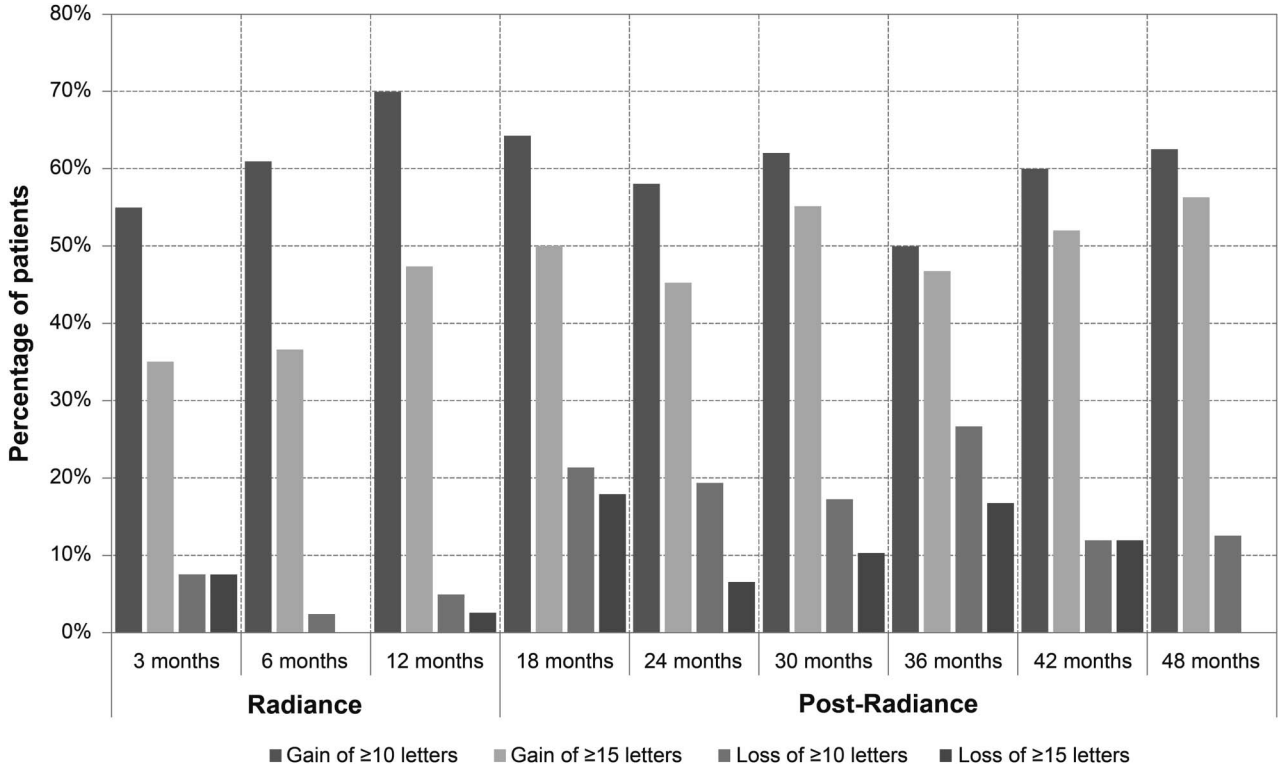

Fig. 5. Categorized BCVA change group at the different time points.

patients (4.9%) had a second recurrence episode. No patients had a third recurrence. Overall, the annualized rate of mCNV recurrences was 0.06 recurrences/year. Two patients (4.9%) reported having mCNV in the fellow eye during the post-RADIANCE follow-up period, however, in both cases the diagnoses was before the post-RADIANCE study. No patients were diagnosed with new mCNV in the fellow eye during the post-RADIANCE observation period.

Treatments Administered

Only seven patients (17.1%) received further treatment during the post-RADIANCE observation period (Group A), of whom four (57.1%) were treated solely with ranibizumab and three (42.9%) switched to other anti-VEGF agents. Six patients (85.7%) received ranibizumab during this period, one (14.3%) received aflibercept, and two (28.6%) received bevacizumab off-label. No patients were treated with vPDT, laser photocoagulation, or any other therapy during this period (Table 3). Patients requiring additional anti-VEGF treatment during the post-RADIANCE observation period received a mean of 5.0 injections (SD 5.9, range 1.0–18.0).

Ocular Adverse Events

Overall, five patients (12.2%) experienced ocular AEs; four patients (9.8%) had mild ocular AEs and two patients (4.9%) had moderate ocular AEs. Seven ocular AEs were reported overall; six were cataracts and one was glaucoma. No ocular AEs were considered serious or related to the anti-VEGF treatment.

Discussion

The RADIANCE trial demonstrated the efficacy and safety of ranibizumab in patients with mCNV over 12 months and consequently ranibizumab became the first anti-VEGF agent approved for the treatment of mCNV. However, long-term data on the treatment of mCNV with ranibizumab, especially within a real-world setting, are lacking. The results presented here demonstrate the long-term effectiveness and safety of ranibizumab for the treatment of mCNV. Patients with mCNV treated with ranibizumab maintained good visual outcomes for up to 48 months of follow-up within clinical practice settings.

The main limitations of our study were its small per country sample size, the low number of patients who completed the final visit at Month 48 and the retrospective nature of the study. Furthermore, since the patients included in this study were a subsample of the East-Asian patients from a randomized clinical trial, the selection criteria in the clinical trial may not be representative of patients with mCNV in the general

Table 2. Frequency, Type, and Annualized Rates of mCNV Recurrence During Post-RADIANCE Observation Period, by Overall Patients and Post-RADIANCE Treatment Group

Variable	Overall (N = 41)	Group A: Required Additional Anti-VEGF (N = 7)	Group B: No Further Treatment (N = 34)
Overall recurrences			
Patients with recurrences, n (%)			
Overall	4 (9.8)	3 (42.9)	1 (2.9)
One mCNV recurrence	2 (4.9)	1 (14.3)	1 (2.9)
Two mCNV recurrences	2 (4.9)	2 (28.6)	0
Recurrence events (overall)			
Total, number of events	6	5	1
Mean (SD), events per patient	0.15 (0.48)	0.71 (0.95)	0.03 (0.17)
Annualized rates, recurrences/ year	0.06	0.23	0.01
Reactivation of a previously regressed mCNV			
Patients with reactivation of mCNV, n (%)			
Overall	2 (4.9)	1 (14.3)	1 (2.9)
One mCNV recurrence	1 (2.4)	0	1 (2.9)
Two mCNV recurrences	1 (2.4)	1 (14.3)	0
Recurrence events (reactivation of mCNV)			
Total, number of events	3	2	1
Mean (SD), events per patient	0.07 (0.35)	0.29 (0.76)	0.03 (0.17)
Annualized rates, recurrences/ year	0.03	0.09	0.01
Newly formed mCNV			
Patients with newly formed mCNV, n (%)			
Overall	2 (4.9)	2 (28.6)	0
One mCNV recurrence	1 (2.4)	1 (14.3)	0
Two mCNV recurrences	1 (2.4)	1 (14.3)	0
Recurrence events (newly formed mCNV)			
Total, number of events	3	3	0
Mean (SD), events per patient	0.07 (0.35)	0.43 (0.79)	0
Annualized rates, recurrences/ year	0.03	0.14	0

mCNV activity was only considered a recurrence if a patient had no evidence of mCNV activity or mCNV treatment during the previous 3 months. Signs of mCNV activity within a period of 3 months were considered part of the previous episode. The annualized rates were defined as the number of events divided by the total person-years.

mCNV, myopic choroidal neovascularization; VEGF, vascular endothelial growth factor.

population. In addition, nine patients received a single vPDT treatment before receiving ranibizumab during the RADIANCE clinical trial. Another limitation of a retrospective study such as this was that post-RADIANCE assessments were taken ±3 months from the time point in question. Intervals between visits for patients not in receipt of treatment were likely to be longer (than those being treated), therefore a broad window was necessary to ensure that these patients had a reasonable potential to contribute data to the assessment points of the study. Although efforts were made to use data collected as close to the time point as possible, this limitation should be considered in the interpretation of the results.

Despite these limitations, our study supports the current data available regarding the long-term effectiveness of anti-VEGF therapies in patients with mCNV. Several studies on the treatment of mCNV with ranibizumab report good visual outcomes over more than 12 months of follow-up,[18,20–26,29,30] but most follow preestablished treatment protocols. A Portuguese case series on 39 eyes reported a mean BCVA gain of 8.0 ETDRS letters after 3 years of follow-up with 35% of patients gaining ≥15 letters after this time period. In their study, 53% of eyes did not require further treatment during the third year of follow-up.[18] In our study, we observed both a greater proportion of patients who no longer required treatment after 12 months and a higher mean visual acuity gain after 48 months. Although caution must be used when drawing comparisons with other studies at this time point, with only 16 patients in our study reaching 48

Table 3. Frequency and Type of Administrations During the Post-RADIANCE Observation Period, by Post-RADIANCE Treatment Group A

Variable	Group A: Required Additional Anti-VEGF (N = 7)
Overall treatment received	
Patients who received further treatment, n (%)	7 (100)
Median number of administrations (range)	3.0 (1.0–18.0)
Mean number of administrations (SD)	5.0 (5.94)
Treatment administered	
Patients who continued ranibizumab monotherapy, n (%)	4 (57.1)
Patients who switched to other anti-VEGF agents, n (%)	3 (42.9)
Ranibizumab intravitreal injection	
Patients who received treatment, n (%)	6 (85.7)
Median number of administrations (range)	2.5 (1.0–6.0)
Mean number of administrations (SD)	3.0 (1.8)
Other anti-VEGF	
Overall	
Patients who received treatment, n (%)	3 (42.9)
Median number of administrations (range)	2.0 (1.0–14.0)
Mean number of administrations (SD)	5.7 (7.2)
Aflibercept	
Patients who received treatment, n (%)	1 (14.3)
Median number of administrations (range)	14.0 (14.0–14.0)
Mean number of administrations (SD)	14.0 (1.0)
Bevacizumab	
Patients who received treatment, n (%)	2 (28.6)
Median number of administrations (range)	1.5 (1.0–2.0)
Mean number of administrations	1.5 (1.00)
Other procedures/treatments	
Patients who received treatment, n (%)	0

VEGF, vascular endothelial growth factor.

months of follow-up, possible reasons for our superior outcomes may be considered. One such reason may be the different ethnicities studied. Our study focused solely on East-Asian patients, whereas the Portuguese study would have consisted primarily of white patients. Evidence from a subgroup analyses of the RADIANCE trial by Holz et al[31] has shown that East-Asian patients tend to achieve higher BCVA gains than white patients over 12 months (17.0 vs. 14.1 letters). Another possible reason may be that a third of the eyes in the Portuguese study had previously received vPDT, compared with 22% of eyes in our study. Eyes treated with vPDT before ranibizumab could achieve a lower gain in BCVA than eyes treated with ranibizumab alone, as demonstrated after 12 months of follow-up in the RADIANCE trial.[16] However, because some studies showed that the therapeutic effect of ranibizumab on mCNV eyes was independent of previous vPDT[30] or even associated with better visual outcomes when used in combination with vPDT,[32] this explanation remains inconclusive.

Other European studies on mCNV treated with ranibizumab have also reported good but lower long-term visual acuity gains compared with our study. A small single-centered Swiss study on 24 eyes by Ladaique et al[21] observed a mean gain of 10 letters after a mean follow-up of 49 months, whereas a case series of 24 eyes by Ruiz-Moreno et al[23] observed a lower mean gain of 4.3 letters after 48 months of follow-up, but no statistically significant improvement was demonstrated after 48 months.[24]

Several Asian studies have reported good visual gains in mCNV eyes treated with ranibizumab over 2 years.[22,25] One Chinese study on 54 eyes observed a substantial mean gain of 17 letters after a mean follow-up of 31.9 months, with 55.5% of patients treated gaining more than 15 letters over this time.[26] The mean BCVA gain was higher than our observed BCVA gain after 30 months of follow-up, but similar to what we reported after 48 months of follow-up. This similarity is interesting considering that the mean baseline BCVA in the Chinese study (30.4 ± 15.9 letters) (20/250) was much lower compared with that in our study. A number of studies have shown that patients with lower initial BCVA exhibit greater visual gains with anti-VEGF treatment, but a higher baseline BCVA can result in a higher final BCVA after treatment.[19,22,33,34] Furthermore, some studies have shown that age at baseline is negatively associated with both BCVA outcome and BCVA change in patients with mCNV after treatment with anti-VEGF therapy.[23,33] In the Chinese study, the mean baseline age was 10 years younger than in our study.

To our knowledge, only one other study has demonstrated the long-term outcomes of patients with mCNV treated with ranibizumab within a clinical practice setting. As in our study, Cohen et al[29] retrospective analyses of 51 patients in a tertiary care center in France did not follow preestablished follow-up treatment protocols. However, unlike our study, patients previously treated with vPDT were excluded and only patients treated with ranibizumab were

included. Cohen et al reported a mean visual gain of 7.6 ± 15.6 letters after a mean follow-up of 39.3 ± 11.3 months but also found that 41% of eyes experienced a decline in BCVA during the follow-up period.[29] Although we did not assess the overall proportion of eyes that experienced a relative decline in visual acuity during the follow-up period, we did find that only 12.5% of patients lost 10 letters or more after 48 months.

Although patients were treated according to the retreatment criteria defined in the RADIANCE study protocol during the first 12 months, from 12 months to 48 months patients were treated at the discretion of their ophthalmologist. The number of mCNV recurrences during this period was low and demonstrated that patients treated with ranibizumab rarely required retreatment. Patients who developed mCNV recurrences received further treatment after 12 months (Group A). This suggests that they may have had a more aggressive disease than those who required no further treatment (Group B), which may explain their relatively lower visual acuity gains. However, studies have shown that despite the suppression of mCNV, the long-term visual acuity outcome of affected eyes treated with anti-VEGF agents was dependent on the progression of macular atrophy,[35–37] which was not assessed in this study. Alternatively, the lower visual acuity gain may simply be due to Group A patients having a higher initial BCVA than Group B patients and thus had less scope for improvement with treatment. Furthermore, a higher proportion of Group A patients was previously treated with vPDT during the RADIANCE trial compared with Group B patients. As mentioned above, patients who were treated with vPDT during the RADIANCE trial experienced lower visual acuity gains after 12 months than patients treated only with ranibizumab.[16] However, caution must be used when interpreting the disparities in visual acuity gain between the groups due to the low number of patients who required further treatment.

At 36 months, the change in mean visual acuity from baseline was not statistically significant; this result seems to be driven by those patients who required further treatment. This finding is unusual, considering the increase in visual acuity which followed from Month 36 to 48.[38] After 36 months, we observed a continued rise in visual acuity. These findings are in contrast to those of a long-term retrospective study on 13 eyes by Martins et al who attributed their observed fall in visual acuity after 36 months to the development of macular atrophy around the regressed mCNV.[36] However, because we did not assess macular atrophy progression nor other treatments that may have influenced visual acuity outcome during the course of our study (e.g., cataract extraction), the reasons for this upward trend in visual acuity cannot be interpreted.

We found that few injections of ranibizumab were sufficient to provide long-term improvement in BCVA in mCNV eyes. This was in accordance with other studies that demonstrated good visual outcomes using a low number of ranibizumab injections.[39,40] Indeed, a study by Kung et al found that visual outcome was similar regardless of whether mCNV eyes were treated with a single ranibizumab injection followed by treatment on a pro re nata basis or with a loading dose of three monthly injections plus pro re nata treatment.[41] However, a much lower rate of retreatment was found in patients who had this loading dose.

No new safety concerns were observed during the post-RADIANCE observation period and the low incidence of ocular AEs, of which none were considered to be related to the anti-VEGF therapy received, supports the well-known safety profile of ranibizumab in clinical practice. However, safety conclusions should be interpreted with caution due to the limited sample size.

In conclusion, BCVA gained at the end of the RADIANCE study was generally sustained over an additional 36 months of follow-up in East-Asian patients in clinical practice settings. Most patients did not require any further anti-VEGF treatment during this time, and no new safety concerns were observed.

Key words: RADIANCE, myopic choroidal neovascularization, ranibizumab.

References

1. 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;157:9–25.e12.
2. Avila MP, Weiter JJ, Jalkh AE, et al. Natural history of choroidal neovascularization in degenerative myopia. Ophthalmology 1984;91:1573–1581.
3. Neelam K, Cheung CM, Ohno-Matsui K, et al. Choroidal neovascularization in pathological myopia. Prog Retin Eye Res 2012;31:495–525.
4. Secretan M, Kuhn D, Soubrane G, et al. Long-term visual outcome of choroidal neovascularization in pathologic myopia: natural history and laser treatment. Eur J Ophthalmol 1997;7: 307–316.
5. Yoshida T, Ohno-Matsui K, Ohtake Y, et al. Long-term visual prognosis of choroidal neovascularization in high myopia: a comparison between age groups. Ophthalmology 2002;109:712–719.
6. Yoshida T, Ohno-Matsui K, Yasuzumi K, et al. Myopic choroidal neovascularization: a 10-year follow-up. Ophthalmology 2003;110:1297–1305.
7. Blinder KJ, Blumenkranz MS, Bressler NM, et al. Verteporfin therapy of subfoveal choroidal neovascularization in pathologic myopia: 2-year results of a randomized clinical trial–VIP report no. 3. Ophthalmology 2003;110:667–673.

8. Group ViPTS. Photodynamic therapy of subfoveal choroidal neovascularization in pathologic myopia with verteporfin. 1-year results of a randomized clinical trial–VIP report no. 1. Ophthalmology 2001;108:841–852.
9. Wong TY, Ohno-Matsui K, Leveziel N, et al. Myopic choroidal neovascularisation: current concepts and update on clinical management. Br J Ophthalmol 2015;99:289–296.
10. Zhou L, Xing YQ, Li T, et al. Meta-analysis of best corrected visual acuity after treatment for myopic choroidal neovascularisation. Int J Ophthalmol 2014;7:720–725.
11. El Matri L, Chebil A, Kort F. Current and emerging treatment options for myopic choroidal neovascularization. Clin Ophthalmol 2015;9:733–744.
12. Munk MR, Ruckert R, Zinkernagel M, et al. The role of anti-VEGF agents in myopic choroidal neovascularization: current standards and future outlook. Expert Opin Biol Ther 2016;16:477–487.
13. Erol MK, Ozdemir O, Coban DT, et al. Ranibizumab treatment for choroidal neovascularization secondary to causes other than age-related macular degeneration with good baseline visual acuity. Semin Ophthalmol 2014;29:108–113.
14. European Medicines Agency. Lucentis: Summary of Product Characteristics Lucentis 10 mg/mL solution for injection. Novartis 2015. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000715/WC500043546.pdf. Accessed May 18, 2016.
15. Muether PS, Hermann MM, Viebahn U, et al. Vascular endothelial growth factor in patients with exudative age-related macular degeneration treated with ranibizumab. Ophthalmology 2012;119:2082–2086.
16. 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;121:682–692.e2.
17. Tufail A, Narendran N, Patel PJ, et al. Ranibizumab in myopic choroidal neovascularization: the 12-month results from the REPAIR study. Ophthalmology 2013;120:1944–1945.e1.
18. Franqueira N, Cachulo ML, Pires I, et al. Long-term follow-up of myopic choroidal neovascularization treated with ranibizumab. Ophthalmologica 2012;227:39–44.
19. Freitas-da-Costa P, Pinheiro-Costa J, Carvalho B, et al. Anti-VEGF therapy in myopic choroidal neovascularization: long-term results. Ophthalmologica 2014;232:57–63.
20. Hefner L, Riese J, Gerding H. Three years follow-up results of ranibizumab treatment for choroidal neovascularization secondary to pathologic myopia. Klin Monbl Augenheilkd 2013;230:401–404.
21. Ladaique M, Dirani A, Ambresin A. Long-term follow-up of choroidal neovascularization in pathological myopia treated with intravitreal ranibizumab. Klin Monbl Augenheilkd 2015;232:542–547.
22. Lai TY, Luk FO, Lee GK, et al. Long-term outcome of intravitreal anti-vascular endothelial growth factor therapy with bevacizumab or ranibizumab as primary treatment for subfoveal myopic choroidal neovascularization. Eye (Lond) 2012;26:1004–1011.
23. Ruiz-Moreno JM, Arias L, Montero JA, et al. Intravitreal anti-VEGF therapy for choroidal neovascularisation secondary to pathological myopia: 4-year outcome. Br J Ophthalmol 2013;97:1447–1450.
24. Ruiz-Moreno JM, Montero JA, Araiz J, et al. Intravitreal anti-vascular endothelial growth factor therapy for choroidal neovascularization secondary to pathological mypoia: six years outcome. Retina 2015;35:2450–2456.
25. Wu TT, Kung YH. Two-year outcome of intravitreal injections of ranibizumab for myopic choroidal neovascularization. J Ocul Pharmacol Ther 2014;30:837–841.
26. Yang X, Dai H. Intravitreal ranibizumab for the treatment of pathological myopia associated with choroidal neovascularization in Chinese patients. Chin Med J (Engl) 2014;127:2906–2910.
27. Gregori NZ, Feuer W, Rosenfeld PJ. Novel method for analyzing Snellen visual acuity measurements. Retina 2010;30:1046–1050.
28. Schulze-Bonsel K, Feltgen N, Burau H, et al. Visual acuities "hand motion" and "counting fingers" can be quantified with the Freiburg visual acuity test. Invest Ophthalmol Vis Sci 2006;47:1236–1240.
29. Cohen SY, Nghiem-Buffet S, Grenet T, et al. Long-term variable outcome of myopic choroidal neovascularization treated with ranibizumab. Jpn J Ophthalmol 2015;59:36–42.
30. Pece A, Milani P, Monteleone C, et al. A randomized trial of intravitreal bevacizumab vs. ranibizumab for myopic CNV. Graefes Arch Clin Exp Ophthalmol 2015;253:1867–1872.
31. Holz FG, Tufail A, Leveziel N, et al. Ranibizumab in myopic choroidal neovascularization: a subgroup analysis by ethnicity, age, and ocular characteristics in RADIANCE. Ophthalmologica 2016;236:19–28.
32. Rishi P, Rishi E, Bhende M, et al. Comparison of photodynamic therapy, ranibizumab/bevacizumab or combination in the treatment of myopic choroidal neovascularisation: a 9-year-study from a single centre. Br J Ophthalmol 2016;100:1337–1340.
33. Gharbiya M, Cruciani F, Parisi F, et al. Long-term results of intravitreal bevacizumab for choroidal neovascularisation in pathological myopia. Br J Ophthalmol 2012;96:1068–1072.
34. Yoon JU, Kim YM, Lee SJ, et al. Prognostic factors for visual outcome after intravitreal anti-VEGF injection for naive myopic choroidal neovascularization. Retina 2012;32:949–955.
35. Farinha CL, Baltar AS, Nunes SG, et al. Progression of myopic maculopathy after treatment of choroidal neovascularization. Ophthalmologica 2014;231:211–220.
36. Martins A, Farhina C, Santos AR, et al. Efficacy and progression of macular atrophy after seven years of treatment with ranibizumab: the myopic CNV seven-up. Oftalmologia 2016;40:35–42.
37. Ohno-Matsui K, Jonas JB, Spaide RF. Macular bruch membrane holes in choroidal neovascularization-related myopic macular atrophy by swept-source optical coherence tomography. Am J Ophthalmol 2016;162:133–139.e1.
38. Wang J, Kang Z. Summary of prognostic factors for choroidal neovascularization due to pathological myopia treated by intravitreal bevacizumab injection. Graefes Arch Clin Exp Ophthalmol 2012;250:1717–1723.
39. Iacono P, Parodi MB, Papayannis A, et al. Intravitreal ranibizumab versus bevacizumab for treatment of myopic choroidal neovascularization. Retina 2012;32:1539–1546.
40. Iacono P, Parodi MB, Papayannis A, et al. A new treatment algorithm for the management of myopic choroidal neovascularization using intravitreal ranibizumab. Acta Ophthalmol 2015;93:e519–e520.
41. Kung YHWT, Huang YH. One-year outcome of two different initial dosing regimens of intravitreal ranibizumab for myopic choroidal neovascularization. Acta Ophthalmol 2014;92:615–620.