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Intravitreal Aflibercept Injection in Patients with Myopic Choroidal Neovascularization

The MYRROR Study

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Purpose: To evaluate intravitreal aflibercept 2 mg in patients with myopic choroidal neovascularization (CNV).

Design: An international, phase III, multicenter, randomized, double-masked, sham-controlled study.

Participants: Patients aged ≥18 years with high myopia (≤−6.0 diopters or axial length of ≥26.5 mm), active myopic CNV, and best-corrected visual acuity (BCVA) of 73–35 Early Treatment Diabetic Retinopathy Study letters in the study eye were included.

Methods: Patients were randomized 3:1 to intravitreal aflibercept or sham. In the intravitreal aflibercept arm, patients received 1 injection at baseline. Additional injections were performed in case of CNV persistence or recurrence at monthly visits through week 44. In the sham arm, patients received sham injections through week 20. At week 24, after assessment of the primary efficacy end point, sham patients received a mandatory intravitreal aflibercept injection followed by intravitreal aflibercept (if disease persisted/recurred) or sham injection every 4 weeks.

Main Outcome Measures: Mean change in BCVA from baseline to week 24.

Results: A total of 122 patients were randomized to intravitreal aflibercept (n = 91) or sham (n = 31). Baseline demographics were similar across groups. At week 24, patients in the intravitreal aflibercept and sham groups gained 12.1 and lost 2 letters, respectively ($P < 0.0001$). By week 48, patients in the intravitreal aflibercept and sham/intravitreal aflibercept groups gained 13.5 and 3.9 letters. Patients in the intravitreal aflibercept group received 2 injections (median) in the first study quarter (week 0–8). Median number of injections in quarters 2 to 4 was 0. Patients in the "sham/intravitreal aflibercept" group received 2 and 1 (median) intravitreal aflibercept injections in quarters 3 and 4. Central retinal thickness improved in parallel with visual gains. Incidence of ocular adverse events was similar in both groups through week 48 (37.4% vs. 38.7); most were assessed by investigators as mild. No deaths occurred.

Conclusions: Intravitreal aflibercept 2 mg was effective for treatment of myopic CNV with clinically important visual and anatomic benefits achieved with a limited number of injections given in the first 8 weeks of treatment. No new safety concerns occurred with treatment. Intravitreal aflibercept should be considered as a treatment option for myopic CNV. *Ophthalmology 2015;122:1220-1227* © *2015 by the American Academy of Ophthalmology.*

*Supplemental material is available at www.aaojournal.org.

Pathologic myopia, defined typically as a refractive error of −6.0 diopters or worse spherical equivalent in association with typical degenerative changes of the fundus,[1] is a common cause of visual impairment worldwide. It is estimated to affect 0.9% to 3.1% of the general population,[2–4] with a higher prevalence in East Asia than in other geographic regions.[2,5,6]

An important complication of pathologic myopia is choroidal neovascularization (CNV). Between 5.2% and 11.3% of patients with pathologic myopia will develop myopic CNV.[2] In particular, myopic CNV is a frequent cause of vision impairment in patients aged less than 50 years.[7] Without treatment, the long-term prognosis of myopic CNV is poor,[8,9] and approximately 90% of patients will have a visual acuity (VA) of 20/200 or less after 5 years.

There are a limited number of effective treatments for myopic CNV. Currently available options include laser photocoagulation,[10] surgical excision of the neovascular membrane, and macular translocation[11–13]; however, all demonstrate generally poor long-term outcomes. Although photodynamic therapy with verteporfin[11] was the first treatment to receive regulatory approval for myopic CNV in a number of countries, visual outcomes have been poor.[12]

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Intravitreal injection of an anti-vascular endothelial growth factor (VEGF) therapy, such as bevacizumab, is now widely used for the treatment of myopic CNV and other types of CNV.[13] Although available data on bevacizumab from clinical trials are sparse, they demonstrate substantial benefits of bevacizumab over other standard treatment options.[14–16] Ranibizumab was recently approved in the European Union and Japan for the treatment of visual impairment caused by CNV secondary to pathologic myopia following the results of a randomized, controlled, phase III trial (RADIANCE) supported by data from a prospective open-label phase II trial.[17–19]

A third anti-VEGF therapy, intravitreal aflibercept, has been shown to be effective in "wet" age-related macular degeneration,[20] macular edema after retinal vein occlusion, and diabetic macular edema.[21,22] Intravitreal aflibercept is a novel recombinant fusion protein that also seems to have a favorable risk/benefit profile in patients with diabetic macular edema.[21,23] We report the primary results of a pivotal trial of intravitreal aflibercept in the treatment of myopic CNV.

Methods

Study Design

MYRROR was an international, phase III, multicenter, randomized, double-masked, sham-controlled study to assess the efficacy of intravitreal aflibercept 2.0 mg compared with sham treatment in patients with myopic CNV. MYRROR was conducted between November 2010 and August 2013 and included 20 sites across 5 countries or regions in Asia (Hong Kong, Japan, Republic of Korea, Singapore, and Taiwan). Study investigators are listed in the Appendix (available at www.aaojournal.org).

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by all appropriate institutional review boards and ethics committees. The trial was registered on ClinicalTrials.gov (identifier NCT01249664).

Participants

Patients were eligible for inclusion in the study if they were aged ≥18 years and had high myopia (defined as ≤−6.0 diopters or axial length of ≥26.5 mm). In addition, patients must have had active (as defined by leakage on fluorescein angiography [FA]) subfoveal or juxtafoveal (within 1−199 μm from the center of the fovea) myopic CNV and a best-corrected visual acuity (BCVA) of 73−35 letters (Early Treatment Diabetic Retinopathy Study equivalent of 20/40−20/200) in the study eye at 4 m. All patients were required to provide signed informed consent before entering the study.

The main exclusion criteria included the following: only 1 functional eye; recurrent myopic CNV or aphakia (including pseudophakic patients) in the study eye; a history or presence of CNV with an origin other than pathologic myopia in the study eye; ocular inflammation or external ocular inflammation in the study eye; any iris neovascularization or vitreous hemorrhage in either eye; uncontrolled glaucoma (defined as intraocular pressure ≥25 mmHg on optimal medical regimen); or previous filtration surgery in either eye. Women of childbearing potential who had a positive pregnancy test result during screening or who intended to breastfeed during the study were also excluded from participation.

Treatment Groups and Randomization

Eligible patients were randomized in a 3:1 ratio to receive intravitreal aflibercept or sham control (stratified by country). In the intravitreal aflibercept group, patients were given 1 injection of intravitreal aflibercept 2.0 mg at baseline. Thereafter, intravitreal aflibercept 2.0 mg injections could be administered in case CNV persisted or recurred (based on the assessment of predefined criteria for retreatment) at a maximum frequency of once every 4 weeks through week 44. Re-treatment was allowed in patients who met 1 or more of the following criteria: (1) reduction in VA by ≥5 letters from the previous Early Treatment Diabetic Retinopathy Study examination; (2) increase in central retinal thickness (CRT) >50 μm from the time of the previous examination, new or persistent cystic retinal changes, subretinal fluid, or pigment epithelial detachment, and new or persistent CNV or bleeding; or (3) deemed necessary by the investigator based on his/her clinical impression or diagnostics performed in the context of standard medical care. In case the assessment of retreatment criteria was negative, patients received sham injections only for masking purposes. In the control group, patients were given 1 sham injection followed by repeated sham injections every 4 weeks through week 20 regardless of whether re-treatment criteria were fulfilled or not. At week 24, after assessment of the primary efficacy end point, control patients received the first mandatory intravitreal aflibercept 2.0 mg injection. Thereafter, as in the intravitreal aflibercept group, additional intravitreal aflibercept treatment could be administered from week 28 to week 44 (at a maximum frequency of once every 4 weeks) if CNV persisted or recurred on the basis of the assessment of the aforementioned retreatment criteria.

Study Outcomes

The primary efficacy end point was the mean change in BCVA from baseline to week 24 in patients with myopic CNV receiving intravitreal aflibercept 2.0 mg or sham treatment. The confirmatory key secondary efficacy end point was the proportion of patients receiving intravitreal aflibercept 2.0 mg or sham treatment who gained ≥15 letters at week 24. Exploratory efficacy end points included the following: absolute change or mean change from baseline in CRT (as assessed by optical coherence tomography [OCT] at week 24 and week 48); absolute change in CNV lesion size from baseline (as assessed by FA at week 24 and week 48); the proportion of patients gaining ≥15 letters from baseline at week 48; the proportion of patients gaining ≥10 letters from baseline at week 24 and week 48; leakage from CNV (as assessed by FA from baseline to week 24 and week 48); change in the EuroQol-5 Dimension score from baseline to week 24 and week 48; and change in the 25-item National Eye Institute Visual Function Questionnaire 25 total score from baseline to week 24 and week 48. The OCT examinations were performed on the study eye at all visits and in addition on the fellow eye at screening, week 24, and week 48. The FA examinations were performed at screening and every 12 weeks after the baseline visit. A central reading center reviewed OCT and FA images to ensure standardized evaluation. Treatment exposure was evaluated in terms of the number of injections administered in each group over the 48-week study period.

Overall safety and tolerability were assessed by monitoring adverse events (AEs), physical examinations, electrocardiograms, vital signs, and clinical safety laboratory tests at prespecified time points, and ocular AEs at every study visit.

Statistical Analysis

By assuming a treatment difference of 10 BCVA letters and a standard deviation of 14 letters, under a randomization schedule of

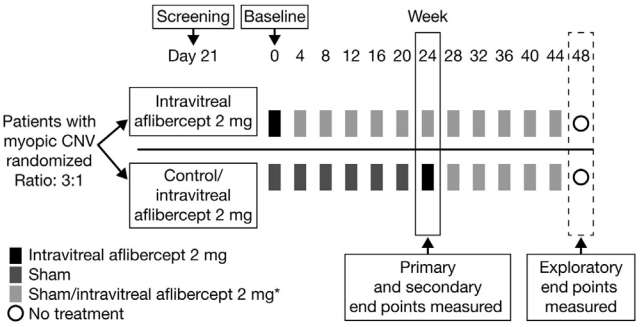

Figure 1. Study design. *If re-treatment criteria were fulfilled. CNV = choroidal neovascularization.

3:1 and using a *t* test with 1-sided alpha level of 0.025, a sample size of 112 patients was estimated to provide 90% power to show a statistical significance with respect to the primary end point. By considering a 5% dropout rate, 120 subjects (90 intravitreal aflibercept and 30 sham) were planned to be randomized. The primary analysis population comprised the full analysis set, which was defined as all randomized patients who received ≥1 study injection (intravitreal aflibercept or sham) and had baseline and ≥1 post-baseline BCVA assessment. The difference in the changes between treatment groups (intravitreal aflibercept minus sham injection) and a 2-sided 95% confidence interval was estimated using an analysis of covariance model, including treatment groups and country/region as fixed effects and baseline BCVA as a covariate. To be able to confirm the superiority of intravitreal aflibercept injection over control sham injection, the lower limit of the 95% confidence interval must have exceeded 0. With the establishment of superiority on the primary end point, the confirmatory secondary efficacy end point—that is, the proportion of patients who gained ≥15 letters—was tested at a 2-sided alpha level of 0.05 by the Cochran–Mantel–Haenszel method weight-adjusted for country/region. All presented data (except CRT) are based on the last observation carried forward approach (least squares [LS] mean difference); observed data (mean difference) are used for CRT. All other variables were tested with descriptive statistics. All statistical analyses were performed using SAS 9.2 (SAS Inc, Cary, NC).

Results

Patient Disposition, Baseline Characteristics, and Exposure

In total, 122 patients were randomized, of whom 91 received intravitreal aflibercept 2.0 mg and 31 received sham (Fig 1); 122 patients were included in the safety set. In the full analysis set, 121 patients were included (90 patients received intravitreal aflibercept 2.0 mg and 31 received sham).

Overall, baseline demographics and clinical characteristics were well balanced between the 2 treatment groups (Table 1). The majority of patients were female (76.0%) and Japanese (74.4%), and the mean age was 58.2±13.3 years. Most patients had classic CNV (98.3%) and a disease duration of <2 months (80.2%). The mean axial length was 28.7 (±1.6) mm.

Overall, patients in the intravitreal aflibercept group received a median of 2.0 (mean, 2.0) injections during weeks 0 to 8 (first quarter) and a median of 0.0 (mean, 0.9, 0.8, and 0.5) intravitreal aflibercept injections during weeks 12 to 44 (for the second, third,

Table 1. Baseline Demographic and Clinical Characteristics: Full Analysis Set

	Intravitreal Aflibercept 2.0 mg (n = 90)	Sham/Intravitreal Aflibercept (n = 31)	Total (N = 121)
Country, n (%)			
Japan	67 (74.4)	23 (74.2)	90 (74.4)
Hong Kong, Singapore, South Korea, Taiwan	23 (25.6)	8 (25.8)	31 (25.6)
Sex, n (%)			
Male	25 (27.8)	4 (12.9)	29 (24.0)
Female	65 (72.2)	27 (87.1)	92 (76.0)
Mean age, yrs ± SD (min–max)	58.5±13.7 (27–83)	57.5±12.1 (27–82)	58.2±13.3 (27–83)
Duration of disease, n (%)			
<2 mos	73 (81.1)	24 (77.4)	97 (80.2)
≥2 mos	17 (18.9)	7 (22.6)	24 (19.8)
Mean BCVA, letters ± SD (min–max)	56.4±9.8 (28–76)	56.6±8.9 (37–70)	56.5±9.5 (28–76)
Mean CRT, μm ± SD (min–max)	349.7±91.3 (147–777)	354.2±107.2 (125–674)	350.9±95.2 (125–777)
Mean IOP, mmHg ± SD (min–max)	15.2±2.7 (8–22)	15.8±2.8 (11–24)	15.4±2.7 (8–24)
Mean axial length, mm ± SD (min–max)	28.8±1.5 (24.5–33.8)	28.6±1.7 (25.3–31.9)	28.7±1.6 (24.5–33.8)
CNV location, n (%)			
Center (subfoveal)	54 (60.0)	20 (64.5)	74 (61.2)
Juxtafoveal, ≤200 μm	35 (38.9)	11 (35.5)	46 (38.0)
Extrafoveal, >200 μm*	1 (1.1)	0	1 (0.8)
Mean CNV size, DA ± SD (min–max)	0.4086±0.5028 (0.008–2.758)	0.3334±0.3413 (0.018–1.851)	0.3894±0.4666 (0.008–2.758)
Type of CNV lesion at screening			
Classic CNV	90 (100.0)	29 (93.5)	119 (98.3)
Classic and occult	0	1 (3.2)	1 (0.8)
Occult	0	1 (3.2)	1 (0.8)

BCVA = best-corrected visual acuity; CNV = choroidal neovascularization; CRT = central retinal thickness; DA = disc area; IOP = intraocular pressure; SD = standard deviation.
*Extrafoveal location of CNV was categorized as major protocol deviation.

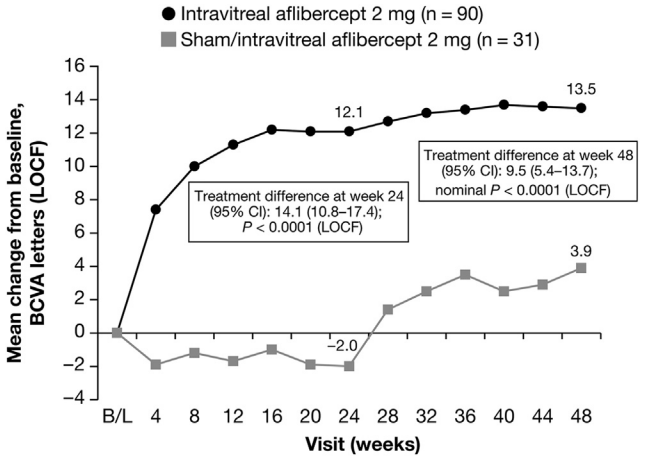

Figure 2. Primary end point: mean change in best-corrected visual acuity (BCVA) (last observation carried forward [LOCF]) from baseline to week 48 — full analysis set. A confirmatory analysis of the primary end point was performed for week 24. Treatment different is least squares (LS) mean change. CI = confidence interval.

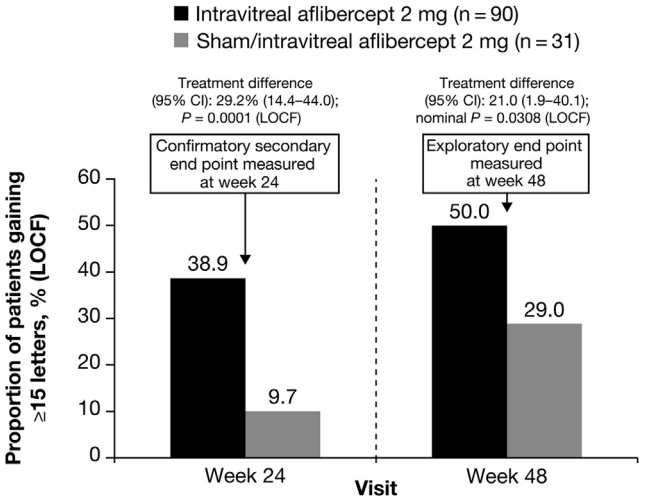

Figure 3. Secondary end point: proportion of patients with ≥15 letters at weeks 24 and 48 — full analysis set. Cochran–Mantel–Haenszel adjusted difference. CI = confidence interval; LOCF = last observation carried forward.

and fourth quarters, respectively). Over the study period of 48 weeks, the median of intravitreal aflibercept injections was 3.0 (mean, 4.2). In the sham/intravitreal aflibercept group, the median number of intravitreal aflibercept injections over the study period was 3.0 (mean, 3.0); the median number of intravitreal aflibercept injections during weeks 24 to 32 (third quarter) and weeks 36 to 44 (fourth quarter) was 2.0 (mean, 1.8) and 1.0 (mean, 1.2), respectively.

Key Outcomes

Primary End Point. For the primary outcome variable (mean change in BCVA from baseline to week 24), patients in the intravitreal aflibercept group had a mean change in BCVA of +12.1 letters compared with a letter loss of 2.0 in the sham group ($P < 0.0001$) (Fig 2).

In a confirmatory analysis of the key secondary end point (proportion of patients who gained ≥15 letters at week 24), a greater proportion of intravitreal aflibercept-treated patients gained ≥15 letters compared with sham-treated patients (38.9% [n = 35] vs. 9.7% [n = 3]; $P = 0.0001$) (Fig 3).

Other Vision End Points. At week 48, patients in the intravitreal aflibercept group had a greater improvement in BCVA than those in the sham/intravitreal aflibercept group, gaining 13.5 versus 3.9 letters, respectively (nominal $P < 0.0001$) (Fig 2). In addition, a greater proportion of patients in the intravitreal aflibercept group gained ≥15 letters from baseline compared with sham/intravitreal aflibercept-treated patients (50.0% [n = 45] vs. 29.0% [n = 9], respectively; nominal $P = 0.03$) (Fig 3).

At week 24, a greater proportion of intravitreal aflibercept-treated patients gained ≥10 (63.3% [n = 57] vs. 12.9% [n = 4]; nominal $P < 0.0001$) and ≥5 (83.3% [n = 75] vs. 19.4% [n = 6]; nominal $P < 0.0001$) letters from baseline compared with sham-treated patients, respectively. At week 48, these numeric differences decreased, because patients in the sham/intravitreal aflibercept group could also receive active treatment from week 24 to 44. In the intravitreal aflibercept and sham/intravitreal aflibercept groups, 68.9% (n = 62) versus 41.9% (n = 9) of patients gained ≥10 letters (nominal $P = 0.0075$), respectively, and 87.8% (n = 72) versus 45.2% (n = 14) of patients gained ≥5 letters (nominal $P < 0.0001$), respectively.

Anatomic Outcomes

At week 24, intravitreal aflibercept-treated patients had a substantially larger mean decrease in CRT than sham patients (−80.7 vs. −13.9; LS mean treatment difference [95% confidence interval]: −67.7 μm [−94.3 to −41.1]; observed cases, $P < 0.0001$). However, by week 48 (after sham patients had switched to intravitreal aflibercept at week 24), the difference in the decrease in CRT between the intravitreal aflibercept–treated patients and sham/intravitreal aflibercept–treated patients was small and not statistically significant (−86.2 vs. −74.0; LS mean treatment difference [95% confidence interval]: −11.2 μm [−37.2 to 14.8]; observed cases, $P = 0.39$) (Fig 4).

In intravitreal aflibercept-treated patients, mean CNV size decreased by −0.24 disc areas (DAs) (from baseline) at week 24. In comparison, CNV size increased by +0.31 DA (from baseline) in sham-treated patients (nominal $P < 0.0001$). Similarly, at

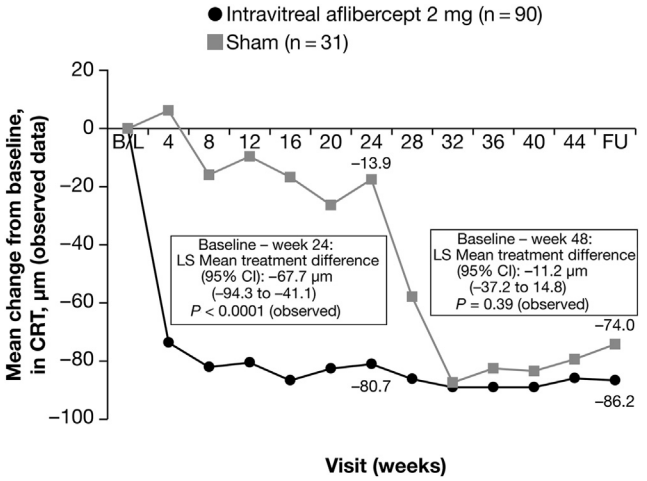

Figure 4. Secondary end point: Mean change in central retinal thickness (CRT) from baseline to week 24 and to week 48 — full analysis set. CI = confidence interval; FU = follow-up; LS = least squares.

Table 2. Overall Adverse Event Profile − Safety Analysis Set (Week 0–48)

	Intravitreal Aflibercept 2.0 mg n = 91	Sham/Intravitreal Aflibercept n = 31	Total N = 122
Patients, n (%)			
Any AE	65 (71.4)	20 (64.5)	85 (69.7)
Any TEAE	64 (70.3)	18 (58.1)	82 (67.2)
Any treatment-related TEAE	9 (9.9)	2 (6.5)	11 (9.0)
Any injection-related TEAE	18 (19.8)	4 (12.9)	22 (18.0)
Any procedure-related TEAE	12 (13.2)	0	12 (9.8)
Any ocular TEAE	34 (37.4)	12 (38.7)	46 (37.7)
Maximum intensity			
Mild	30 (33.0)	12 (38.7)	42 (34.4)
Moderate	3 (3.3)	0	3 (2.5)
Severe	1 (1.1)	0	1 (0.8)
Any ocular TEAE on study eye	29 (31.9)	11 (35.5)	40 (32.8)
Treatment-related	6 (6.6)	1 (3.2)	7 (5.7)
Injection-related	18 (19.8)	4 (12.9)	22 (18.0)
Procedure-related	6 (6.6)	0	6 (4.9)
Any SAEs	7 (7.7)	1 (3.2)	8 (6.6)
Treatment/injection/procedure-related	1/1/1 (1.1)	0/0/0 (0.0)	1/1/1 (0.8)
Any death	0	0	0

AE = adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

week 48, intravitreal aflibercept-treated patients had a greater decrease in CNV size (from baseline) than sham/intravitreal aflibercept-treated patients, although the difference was less pronounced (−0.21 vs. −0.06 DA, respectively; nominal $P = 0.3$).

In addition, the area of fluorescein dye leakage was significantly reduced in intravitreal aflibercept-treated patients compared with those receiving sham (small increase observed) at week 24 (LS mean change: −0.48 vs. 0.19 DA, respectively; nominal $P < 0.0001$) and compared with those receiving sham/intravitreal aflibercept at week 48 (LS mean change: −0.50 vs. −0.20 DA, respectively; nominal $P < 0.0001$). At week 48, 86.4% (n = 76) of patients in the intravitreal aflibercept group and 66.7% (n = 20) of patients in the sham/intravitreal aflibercept group had no active CNV leakage (full analysis set, last observation carried forward).

Quality of Life Outcomes

The differences in the vision-related quality of life (National Eye Institute Visual Function Questionnaire 25) total scores at week 24 and week 48 between patients treated with intravitreal aflibercept and those treated with sham were statistically significant (data not shown). There were also statistically significant differences in the EuroQol-5 Dimension score between the 2 treatment groups (in favor of intravitreal aflibercept) at week 48 but not week 24 (data not shown).

Safety

Overall, 7 patients (5.7%) (all in the intravitreal aflibercept-treated group) experienced a serious treatment-emergent AE (TEAE). In total, 4 (4.4%) nonocular and 3 (3.3%) ocular serious AEs were reported by patients in the intravitreal aflibercept group; of these, only 1 ocular serious AE (a macular hole) occurred in a study eye. There was 1 (1.1%) arterial thromboembolic event (cerebral hemorrhage; as defined by the Antiplatelet Trialists' Collaboration) in the intravitreal aflibercept-treated group. This event occurred in a patient diagnosed with hypertension and was not considered by the investigator to be related to study drug, injection, or study procedures. No deaths were reported in either treatment group over 48 weeks.

The incidence of ocular TEAEs was similar in the intravitreal aflibercept and sham/intravitreal aflibercept group (37.4% vs. 38.7%, respectively) over 48 weeks of treatment (Table 2); in addition, most of the reported ocular TEAEs in the intravitreal aflibercept and sham/intravitreal aflibercept groups were considered to be of mild intensity (33.0% vs. 38.7%, respectively), resolved within the study period, and did not lead to the interruption or permanent discontinuation of study treatment.

The most frequently reported (≥5%) ocular TEAEs in the study eye were conjunctival hemorrhage (11.0%), eye pain (7.7%), and punctate keratitis (6.6%) in the intravitreal aflibercept group and punctate keratitis (12.9%), dry eye (6.5%), and posterior capsule opacification (6.5%) in the sham/intravitreal aflibercept group (Table 3).

Discussion

MYRROR is the first phase III randomized controlled trial of intravitreal aflibercept in patients with visual impairment due to myopic CNV, providing a high level of clinical trial evidence for statistically significant and clinically important improvements in visual and anatomic parameters compared with sham/intravitreal aflibercept injection over 48 weeks. To date, the use of other anti-VEGF drugs in patients with myopic CNV has been evaluated mainly in several small uncontrolled studies. The RADIANCE study provided the first level 1 evidence[21] that ranibizumab resulted in rapid improvements in VA in patients with myopic CNV that were statistically superior to verteporfin photodynamic therapy after month 3.

In the MYRROR phase III trial, an initial single intravitreal aflibercept injection was followed by additional injection treatments every 4 weeks if individual assessments of patients showed that CNV persisted or recurred according to predefined criteria. Because verteporfin photodynamic therapy was not approved for myopic CNV (other than CNV

Table 3. Most Frequent (≥5%) Ocular and Nonocular Treatment-Emergent Adverse Events — Safety Analysis Set (Week 0–48)

Preferred Term*	Intravitreal Aflibercept 2.0 mg n = 91	Sham/Intravitreal Aflibercept n = 31	Total N = 122
Patients with any ocular TEAE in the study eye, n (%)	29 (31.9)	11 (35.5)	40 (32.8)
Conjunctival hemorrhage	10 (11.0)	1 (3.2)	11 (9.0)
Punctate keratitis	6 (6.6)	4 (12.9)	10 (8.2)
Eye pain	7 (7.7)	1 (3.2)	8 (6.6)
Dry eye	2 (2.2)	2 (6.5)	4 (3.3)
Posterior capsule opacification	0 (0.0)	2 (6.5)	2 (1.6)
Patients with any nonocular TEAE, n (%)	53 (58.2)	12 (38.7)	65 (53.3)
Nasopharyngitis	17 (18.7)	3 (9.7)	20 (16.4)
Headache	6 (6.6)	1 (3.2)	7 (5.7)
Nausea	7 (7.7)	0 (0.0)	7 (5.7)
Dizziness	5 (5.5)	0 (0.0)	5 (4.1)

TEAE = treatment-emergent adverse event.
*MedDRA version 16.0.

associated with age-related macular degeneration) in the main study country, Japan, at the inception of the MYRROR study, and was not widely considered a standard-of-care therapy because of its limited efficacy, a sham treatment was chosen for the control group of MYRROR. For both the primary (mean change in BCVA from baseline to week 24) and the confirmatory secondary end point (proportion of patients who gained ≥15 letters at week 24), intravitreal aflibercept was statistically superior to sham. For both end points, clinically meaningful improvements were achieved with intravitreal aflibercept with a mean BCVA change of +12.1 letters seen (vs. −2.0 letters with sham) and 38.9% of patients gaining ≥15 letters from baseline (vs. 9.7% with sham) at week 24. Furthermore, these changes were sustained and even slightly increased to the end of follow-up (+13.5 letters and 50% gaining ≥15 letters at week 48).

Thus, a treatment regimen with 1 initial intravitreal aflibercept injection followed by re-treatment only in case of persistence or recurrence of the CNV provided rapid and sustained visual benefits for patients with myopic CNV. In contrast to previous results with verteporfin photodynamic therapy in the Verteporfin in Photodynamic Therapy (VIP) study, which showed only visual stabilization compared with sham,[14] in the MYRROR study intravitreal aflibercept provided sustained and clinically meaningful visual improvements over the entire observation period of 48 weeks.

Patients in the sham/intravitreal aflibercept group received sham injections through week 20 and were injected with intravitreal aflibercept for the first time at week 24. Although this control group experienced visual benefits (improvement of +5.9 letters from week 24 to week 48), the changes were numerically not as marked as in those patients who received intravitreal aflibercept treatment when comparing the first 24 weeks of treatment for both arms (week 0–24 for the intravitreal aflibercept group [+12.1 letters] and week 24–48 for the sham/intravitreal aflibercept group). These numeric differences in mean visual gains support early initiation of treatment after diagnosis of active myopic CNV to achieve the maximum visual benefits for an individual patient. Accordingly, it may be considered beneficial to instruct patients with pathologic myopia not to delay control assessments in case of any visual deterioration.

Additional exploratory analyses of VA gains in both treatment groups (intravitreal aflibercept and sham/intravitreal aflibercept) through week 48 supported the findings of the primary and confirmatory secondary efficacy analyses. Most notable, vision benefits were maintained (and slightly increased extended) despite the fact that most injections were given in the first 8 weeks after initiation of intravitreal aflibercept injections in both treatment groups, with minimal subsequent re-injections. This underscores that the nature of myopic CNV is such that it can be managed with a limited number of injections in the early course of treatment. In this respect, myopic CNV is different from other indications for anti-VEGF therapeutics, such as neovascular "wet" age-related macular degeneration or diabetic macular edema, for which ongoing, proactive treatment is required to achieve sustainable and optimal efficacy.[20]

In the current study, mean age, female-to-male ratio, refractive error, and axial length were typical for patients with myopic CNV, and thus these findings seem to be representative of the general population of patients with myopic CNV.[2,18,19]

Patients in the MYRROR study had exclusively Asian ethnicity because the trial was only conducted in East-Asian countries; however, myopic CNV is also prevalent in other geographic regions outside of Asia. Because existing epidemiologic and clinical data show only differences in prevalence figures between different geographic regions but no other clinically relevant differences in natural history[2] or different outcomes with other anti-VEGF therapies, such as ranibizumab treatment,[19] it may be inferred that the results of the MYRROR study are also relevant to patients with myopic CNV outside of Asia.

Intravitreal aflibercept was generally well tolerated in patients with myopic CNV. The observed safety profile was similar to what is known for intravitreal aflibercept over 12 months.[21,22,24–27] There was a slightly higher incidence of AEs in the intravitreal aflibercept group. This

may be related in part to the 3:1 randomization ratio, because most TEAEs were rare and rarer TEAEs may not occur in smaller treatment groups. However, the difference in AE frequencies was largely driven by administering penetrating injections, which were recorded as injection- or procedure-related events. Such events were generally of mild intensity and were more frequent in the intravitreal aflibercept group. Overall, the AEs observed showed no pattern and were not typically due to the systemic pharmacodynamic effects of systemically given anti-VEGF drugs. Of note, there were no events of intraocular inflammation or endophthalmitis.

Currently, experience with intravitreal aflibercept in myopic CNV is limited to a maximum follow-up period of 48 weeks, and for de novo patients only. It will be important to observe whether VA continues to be maintained after the initial intravitreal aflibercept treatment in daily clinical practice or whether other, myopia-related pathologies (independent of myopic CNV), such as chorioretinal atrophy, may have a long-term effect on vision.

In conclusion, in this study, intravitreal aflibercept 2.0 mg was shown to be a well-tolerated and effective treatment for patients with myopic CNV. Visual improvements and anatomic benefits were maintained and extended from week 24 to 48. The nature of myopic CNV is such that it may be successfully treated with an active treatment regimen of intravitreal aflibercept 2.0 mg with a limited number of injections early in the course of treatment. Intravitreal aflibercept seems to be a promising first-line treatment option in patients with myopic CNV.

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Abbreviations and Acronyms:
AE = adverse event; **BCVA** = best-corrected visual acuity; **CNV** = choroidal neovascularization; **CRT** = central retinal thickness; **DA** = disc area; **FA** = fluorescein angiography; **LS** = least squares; **OCT** = optical coherence tomography; **TEAE** = treatment-emergent adverse event; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor.

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