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VISUAL ACUITY OUTCOMES OF RANIBIZUMAB TREATMENT IN PATHOLOGIC MYOPIC EYES WITH MACULAR RETINOSCHISIS AND CHOROIDAL NEOVASCULARIZATION

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Purpose: To investigate visual and morphological outcome in eyes with MRS and choroidal neovascularization (CNV) secondary to pathologic myopia treated with intravitreal (IVT) ranibizumab.

Methods: Post hoc analysis of the patients included in the RADIANCE trial (n = 277) was performed to evaluate the impact of MRS on the functional outcome in patients with myopic choroidal neovascularization (mCNV) undergoing intravitreal ranibizumab injections.

Results: Prevalence of MRS in pathologic myopia population is 6%. Respective patients were generally older than patients without MRS. Study eyes with MRS at baseline (BL) showed an initially poor treatment response after 3 months (mean change in best corrected visual acuity (BCVA) was 2.8 ± 12.4 letters, $P = 0.009$). After 12 months of treatment however, the mean change in BCVA was 7.1 ± 14.5 early treatment diabetic retinopathy study (ETDRS) letters ($P = 0.025$). Patients with MRS at baseline received more intravitreal injections than the other RADIANCE patients without MRS (MRS, n = 15 eyes: 5.8 ± 2.1 vs. RADIANCE non-MRS [n = 207 eyes]: 4.0 ± 2.9; $P = 0.0001$).

Conclusion: Improvement of visual acuity is delayed and reduced after 3 months intravitreal ranibizumab in eyes with MRS and myopic choroidal neovascularization compared to eyes without MRS. More ranibizumab injections are needed in eyes with MRS to gain comparable BCVA at Month 12.

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Myopia is one of the leading causes of visual impairment worldwide.[1–7] Myopic choroidal neovascularization (mCNV) is a common vision-threatening complication of pathologic myopia. Intravitreal anti-vascular endothelial growth factor (VEGF) has been shown to effectively improve and maintain vision in patients with mCNV. The efficacy and superiority of ranibizumab in comparison with verteporfin photodynamic therapy (vPDT) have been shown in the RADIANCE trial and since 2014 anti-VEGF is approved from Health Authorities for the treatment of subfoveal mCNV.[8,9]

In addition to mCNV, intraretinal splitting of the inner and outer retinal layers resulting in intraretinal cystoid spaces is described in some myopic eyes. This entity is recognized as myopic macular retinoschisis (MRS) and may be best visualized with optical coherence tomography (OCT).[10,11] Myopic macular retinoschisis is probably of degenerative nature and develops spontaneously in eyes with pathologic myopia. In the current study, the baseline OCT scans of both eyes from all 277 patients included in the RADIANCE trial have been reanalyzed for the presence of MRS and it was explored if the presence of MRS affects the visual and morphological outcome of patients with mCNV treated with ranibizumab therapy for mCNV.

Methods

The design of the RADIANCE study has been described in detail elsewhere.[8] The key inclusion criteria of the RADIANCE study were: 1) diagnosis of active CNV secondary to pathologic myopia

confirmed by complete ocular examination; 2) presence of at least one of the following lesion types: a) subfoveolar, b) juxtafoveolar with the involvement of the central macular area, c) extrafoveolar with involvement of the central macular area and d) margin of the optic disk with involvement of the central macular area; 3) BCVA ≥24 and ≤78 ETDRS letters at a starting distance of 4 meters using ETDRS visual chart; and 4) visual loss only because of the presence of any eligible types of CNV related to pathological myopia based on clinical ocular findings, fluorescein angiography, and OCT data.

Main exclusion criteria were: 1) history of stroke, panretinal focal/grid laser photocoagulation with involvement of the macular area, intraocular treatment with corticosteroids and/or intraocular surgery within 3 months before randomization and treatment with anti-VEGF or vPDT at any time in the study eye or hypersensitivity to ranibizumab or verteporfin or to drugs of similar class; 2) presence of CNV secondary to any cause other than pathologic myopia.[8]

Briefly, patients with visual impairment because of myopic CNV were included and randomized to three different treatment groups. Group 1 (n = 106) received ranibizumab on Day 1, Month 1 and thereafter as needed guided by visual acuity (VA) stabilization criteria. Group 2 (n = 116) received ranibizumab on Day 1 and thereafter as needed guided by disease activity criteria, and Group 3 (n = 55) was treated with vPDT on Day 1 and from Month 3 disease activity was treated with ranibizumab and/or vPDT at investigators' discretion (www.clinicaltrials.gov, NCT01217944).

In this study, a post hoc analysis of the patients included in the RADIANCE trial (n = 277) was performed to evaluate the impact of MRS on the functional outcome in patients with mCNV undergoing intravitreal (IVT) ranibizumab injections. Presence of MRS on OCT scans was determined on the first study visit. Epiretinal membrane (ERM) and vitreoretinal traction (VMT) were no exclusion criteria. Optical coherence tomography cross-hair scans and volume scans performed either on time domain or spectral domain OCT were analyzed by two masked, independent graders of the Bern Photographic Reading Center (BPRC) and approved by a third grader. Intraretinal splitting of the inner and outer retinal layers resulting in intraretinal, hyporeflective cystoid spaces on OCT was identified as MRS (Figure 1).[10,11] Splitting within the outer plexiform layer and the outer nuclear layer was recognized as outer MRS. Schisis cavities found at the level of the inner plexiform, ganglion cell layer, and retinal nerve fiber layer were defined as inner MRS.[12,13] The inner nuclear layer defined the neuroretinal boundary between inner and outer retinoschisis. The presence of MRS in the fellow eyes and the development of new MRS in both study and fellow eyes over the 12-month period were evaluated as well to describe the prevalence and incidence of MRS in this study population. Optical coherence tomography scans of the study and fellow eyes were evaluated on a monthly basis. Myopic choroidal neovascularization was diagnosed using fluorescein angiography, which was performed at screening and at the end of the study. For the fellow eyes, inclusion and exclusion criteria of the RADIANCE study were applied with the only exception that mCNV was not requested for the inclusion in the MRS study. Localization of retinoschisis was determined using the standard ETDRS grid on OCTs.

To evaluate the effect of MRS on the treatment outcome of ranibizumab in mCNV, the study eyes of the RADIANCE patients undergoing ranibizumab injections were included in the post hoc visual function analysis, whereas patients previously assigned to the vPDT group were excluded. Best-corrected visual acuity (BCVA) measured in Snellen visual acuity ratios and mean change presented in ETDRS letters was compared between baseline (BL) versus 3 and 12 months of treatment with IVT ranibizumab. Data were analyzed using IBM Statistical software (SPSS 17; IBM Inc, Chicago, IL). Statistical paired *t*-test was used to compare the means. *P*-values ≤0.05 were considered statistically significant. Correlations were performed using Pearson correlation coefficient. Values are given as mean ± SD. Prevalence and incidence of MRS were obtained with descriptive statistics. The research followed the tenets of the Declaration of Helsinki. Institutional Review Board approval was granted.

Results

The RADIANCE study included 277 patients. Optical coherence tomography scans were available

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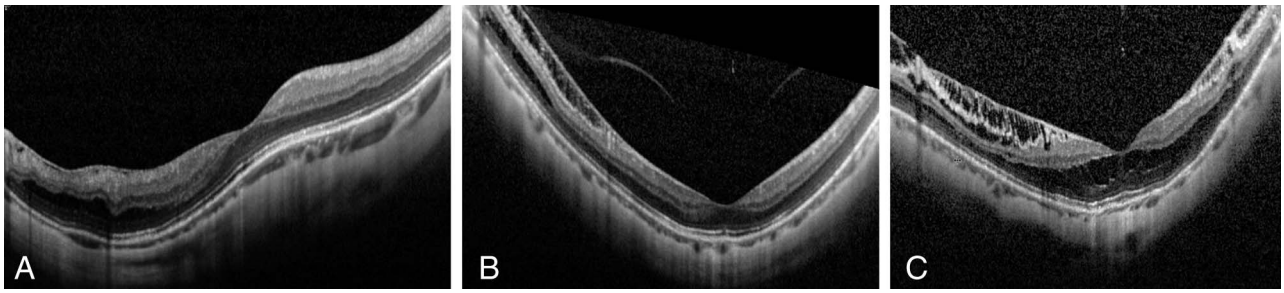

Fig. 1. Two different types of myopic macular retinoschisis: (**A**) example of outer retinoschisis; (**B**) example of inner retinoschisis; (**C**) example of both inner and outer MRS.

for all 277 study eyes and for 197 fellow eyes. Therefore, a total of 474 eyes has been included into this analysis and has been evaluated for the presence and the development of MRS.

The prevalence of MRS was 6% in the RADIANCE population. At BL visit, MRS was present in 6% (28/474 of eyes) with pathologic myopia: 18 study eyes and 10 fellow eyes showed respective alterations and bilateral MRS were found in 4 of those 25 patients. The incidence of MRS in the RADIANCE population was 1.7% after 12 months, as 8 patients developed new onset of this clinical feature (7 in the study eyes and 1 in the fellow eye).

Demographic data and clinical characteristics of patients with and without MRS are presented in Table 1. Patients with MRS were generally older than the patients without MRS (MRS (n = 25 patients): 62 ± 11 versus non-MRS (n = 252 patients): 55 ± 14 years; $P < 0.0001$). Myopic macular retinoschisis was more frequently found in woman (Table 1, $P < 0.0001$).

Mean central retinal thickness (CRT) did not statistically significantly differ between the MRS group (452 ± 275 μm) and the non-MRS group (359 ± 108 μm, $P = 0.34$). There was no correlation between CRT and BCVA (Pearson correlation r = 0.10, $P = 0.54$).

All study eyes had mCNV, whereas only three of the fellow eyes of the MRS group had mCNV at baseline (Table 2). Otherwise, study and fellow eyes with MRS showed no differences in terms of clinical characteristics. Vitreomacular traction was present in two study eyes with MRS but in none of the fellow eyes with MRS. The majority of the eyes with MRS had schisis in the outer retinal layers (15 study eyes and 7 fellow eyes).

Myopic macular retinoschisis was most frequently found (13/28 eyes [46%]) in the inner ETDRS subfields. Details regarding the localization of MRS are presented in Table 2. There was no correlation between location of MRS and location of mCNV (r = 0.24, $P = 0.20$), and there was also no correlation between visual acuity and location of MRS (r = 0.075, $P = 0.66$). During follow-up, new MRS developed in 1.7% (8/474) of high myopic eyes in the outer retinal layers. None of them had vitreoretinal traction, but all of respective eyes showed an ERM at BL. Two fellow eyes with inner retinal schisis at baseline developed outer schisis during follow-up. None of the patients

Table 1. Comparison of Baseline Demographics Data of All RADIANCE Patients With and Without MRS Including Fellow and Study Eyes

	Non-MRS RADIANCE (n = 252 Patients)	MRS (n = 25 Patients)	*P*
Age ± SD (min–max)	55 ± 14 (18–87)	62 ± 11 (45–85)	<0.0001
Gender (n)			<0.0001
Male	65	3	
Female	187	22	
Axial length ± SD	29 ± 2 (26–31)	29 ± 2 (26–36)	0.076
Mean spherical equivalent ± SD (min–max), D	−12 ± −5 (−6 to −30)	−13 ± −6 (−6 to −23)	0.57
BL VA ± SD (min–max), ETDRS letters	61 ± 19 (10–88)	58 ± 20 (8–83)	0.35
Mean Snellen VA	20/120	20/130	
CRT ± SD, μm	359 ± 108	452 ± 275	0.34

BL, baseline; CRT, central retinal thickness; ERM, epiretinal membrane; ETDRS, early treatment diabetic retinopathy study; MRS group, patients who had initially MRS on study- or fellow eye; N, number of eyes; non-MRS, study eyes of patients with mCNV included in the RADIANCE trial; SD, standard deviation; VA, visual acuity; VMT, vitreomacular traction.

Table 2. Characteristics of Study and Fellow Eyes With MRS at Baseline

	Study Eye	Fellow Eye
N = 25 patients	18	10
Gender, n		
Male	3	0
Female	15	10
Mean spherical equivalent ± SD (min–max), D	−13 ± −6 (−6 to −23)	−12 ± −4 (−6 to 18)
Type of MRS, n		
VMT+outer schisis	2	0
Inner schisis	7	3
Outer schisis	15	7
ERM	16	8
mCNV, n	18	3
CNV location		
Subfoveal	7	3
Juxtafoveal	6	0
Extrafoveal	5	0
BL VA ± SD (min–max)	59 ± 19 (33–78)	60 ± 21 (10–83)
Mean Snellen VA	20/130	20/125
MRS location, n		
Central ETDRS subfield	5	2
Inner ETDRS subfield	9	4
Outer ETDRS subfield	4	4

BL, baseline; ERM, epiretinal membrane; ETDRS, early treatment diabetic retinopathy study; N, number of eyes; VA, visual acuity; VMT, vitreomacular traction.

had progression of MRS to a macular hole or foveal detachment during the follow-up period of 12 months. No further changes in terms of MRS were registered during the 12-month follow-up.

Baseline MRS was diagnosed in 18 study eyes. Three of those eyes had been randomly assigned to the vPDT treatment group and were therefore excluded from our visual acuity outcome analysis. Thus, a total of 15 eyes with MRS at BL were treated with 0.5 mg of ranibizumab IVT for active mCNV and were included in our evaluation. Patients' BL BCVA did not significantly differ between the study eyes with (n = 15) or without (n = 207) MRS treated with ranibizumab: 57 ± 21 (mean Snellen visual acuity 20/130) versus 56 ± 13 ETDRS letters (mean Snellen visual acuity 20/150), respectively ($P = 0.53$). At the 3 months, study eyes with MRS (n = 15) had significantly lower visual acuity gain compared to the non-MRS study eyes (n = 207) treated with IVT ranibizumab (2.8 ± 12.4 letters vs. 12.3 ± 9.4 letters [$P = 0.013$] [Table 3]). After 12 months of follow-up, both groups revealed significant improvement in visual acuity: 7.1 ± 14.5 versus 14.4 ± 10.5 ($P = 0.16$). Patients with MRS were treated more frequently with IVT ranibizumab injections over the 12-month period: 5.8 ± 2.1 versus 4.0 ± 2.9 ($P < 0.0001$). Most of the MRS patients treated with IVT ranibizumab have been previously assigned to Group 2 (the "disease activity group") (n = 13), whereas only two MRS patients were treated based on the "visual acuity stabilization criteria."

Study eyes who developed new MRS over time (n = 7) had a comparable visual acuity outcome after 12 months and received a similar number of injections compared to study eyes with MRS at baseline. Two eyes were treated according to the "disease activity" treatment regimen, whereas the remaining mCNV eyes with new onset MRS were treated according to the "visual acuity stabilization" criteria.

Discussion

This is, to best of our knowledge, the biggest study to evaluate the prevalence and functional outcome of MRS in patients with mCNV. Further, it is so far the biggest study to evaluate the treatment efficacy of ranibizumab in this respective patient population. The prevalence and incidence of MRS was 6 and 1.7% in our patient cohort, respectively. This is in line with recently published manuscripts, which reported a prevalence ranging from 6.4 to 14.7%.[7,14] Also, the spherical equivalent and the axial length were very similar between our study population and the recently published data on patients with pathologic myopia and MRS by Henaine-Berra et al[7]: −12.47 ± 4.99 D versus −15.04 ± 5.33 D and 28.67 ± 1.87 mm versus 28.88 ± 2.31 mm, respectively. Our data also confirm

Table 3. Comparison of Visual Outcomes of Eyes With and Without Macular Retinoschisis (MRS) Treated With Intravitreal Ranibizumab for Myopic Choroidal Neovascularization

	Non-MRS Study Eyes (n = 207)	*P* (Compared with BL)	MRS Study Eyes (n = 15)	*P* (Compared with BL)	*P* (Non-MRS vs. MRS Study Eyes)
BL VA, ETDRS letters	56 ± 13		57 ± 21		0.53
Mean Snellen VA	20/150		20/130		
3 months VA gain, ETDRS letters	12.30 ± 9.4	0.0001	2.8 ± 12.4	0.009	0.013
12 months VA gain, ETDRS letters	14.4 ± 10.5	0.0001	7.1 ± 14.5	0.025	0.16
Number of IVT injections	4.0 ± 2.9		5.8 ± 2.1		<0.0001

BL, baseline; ERM, epiretinal membrane; ETDRS, early treatment diabetic retinopathy study; IVT, intravitreal; N, number of eyes; VA, visual acuity; VMT, vitreomacular traction.

previous findings of Takano and Kishi[15] which have shown that MRS was more prevalent in older patients with pathologic myopia.

The pathogenesis of MRS includes various mechanisms.[10–20] Degenerative aging processes within the retina could lead to the development of MRS in eyes with pathologic myopia.[15,16] The weak adhesion between the inner retina and the underlying sclera, the mechanical dissociation attributable to the scleral bowing, and the caving of the retina might facilitate the development of the MRS in and around atrophic areas.[12,15–17]

Vitreous traction and scleral and chorioretinal changes are considered to be causative factors for the formation of retinoschisis,[12,15–19] whereas a dome-shaped macula was deemed a protective factor preventing MRS.[16,17] Although vitreomacular traction was only found in two of our cases with MRS, ERM was found in the majority of our MRS cases. Thus, tractional forces may have been a relevant factor for the formation of MRS in our patient cohort. Another possible explanation for MRS involves degenerative processes of the staphylomatous region in myopic eyes.[15] Optical coherence tomography images of posterior outer retinoschisis in high myopia resemble the histological appearance of typical peripheral microcystoid degeneration. In general, this peripheral cystoid degeneration shows retinal splitting of the outer plexiform layer.[16,20] Consistently, most eyes in our study had schisis in the outer retinal layers and two eyes with initial inner retinal schisis developed outer retinal schisis over time.

Although we identified eight eyes with new onset MRS over the period of 12 months, we did not notice the development of full thickness macular holes or subretinal detachments. The only progressive changes were found in two fellow eyes, which developed outer retinal schisis in preexisting inner MRS. Previous studies reported progression of MRS to full thickness macular holes or foveal detachment and spontaneous improvement, but the majority of the affected eyes were reported to remain stable.[11,16,18,21] The lack of progression to full-thickness macular holes in our study in comparison with previously published studies may have been due to the fact that our observational period was only 12 months. Significant progression of MRS may manifest after a longer follow-up period and the observational period may have been too short to detect the changes. However, a previous study reported full-thickness macular hole formation within a mean follow-up period of 15 months.[22] Another explanation may be found in a possible interaction between mCNV, continuous anti-VEGF treatment, and MRS.

Intravitreal anti-VEGF injections have been previously discussed as a potential risk factor for progression of MRS in myopic eyes with CNV. Huang et al[21] identified aggravation of MRS and an increase of central retinal thickness under ranibizumab treatment in 81 of 83 mCNV patients with preexisting ERM and MRS. Lai et al[23] reported development of macular hole (1/37 eyes) and worsening of MRS (2/37 eyes) after intravitreal injections for mCNV. The authors concluded that respective complications might or might not be related to the application of intravitreal injections.[23] Our patient cohort presented new development of outer MRS in preexisting inner MRS in two fellow eyes, whereas new MRS developed in seven treated, study eyes but only in one, untreated fellow eye. Thus, the higher incidence of new onset MRS in the study eyes may be related to the administration of ranibizumab. None of our study eyes showed MRS aggravation and although their treatment response was rather delayed and a higher number of IVTs were needed compared with the non-MRS mCNV patients, study eyes showed significant and comparable visual function improvement under continuous ranibizumab administration after 12 months. This finding in turn rather suggests a beneficial than a worsening effect

of continuous ranibizumab treatment in this patient cohort. Nevertheless, numerically more study eyes than fellow eyes developed new onset MRS.

Furthermore, the mechanical procedure of injection may influence the vitreomacular interface and may therefore be a contributing factor for the development of MRS in eyes with mCNV, given that the adhesion and traction of the vitreous on the posterior pole can cause MRS and myopic traction maculopathy.[18,24] The injection procedure may induce posterior vitreous detachment in patients with CNV although this is very rare unless there is focal vitreomacular adhesion.[24] Another influencing mechanism might be the shrinkage of the fibrovascular tissue induced by anti-VEGF agents. This contraction might lead to tractional forces and enhance to some degree the separation of the neural retina, which could lead to the onset of MRS.

Myopic macular retinoschisis was most frequently found in the inner ETDRS subfield. There was no correlation between BCVA and location of MRS, which may be best explained by the fact that the presence of mCNV may have a stronger impact on BCVA than MRS.

In our study, almost all the eyes (16/18) with MRS had an ERM at BL. The MRS study eyes received significantly more intravitreal ranibizumab injection when compared with the non-MRS eyes (5.8 ± 2.1 vs. 4.0 ± 2.9, $P < 0.0001$). These facts together with the finding of Huang et al[21] that eyes with MRS aggravation presented an ERM, are highly indicative that ERM is an independent key factor for MRS formation and aggravation. The high prevalence of ERM (89%) in this group may be also causative for the higher treatment need and deferred treatment response in patients with MRS and mCNV. Distribution and penetration of ranibizumab into and throughout retinochoroidal layers may differ in eyes with respective alterations. Further, the tractional force to the retina, leading to interstitial tissue pressure decrease, results in an influx of fluid from the blood vessels and contributes to intraretinal fluid evident in neovascular age-related macular degeneration.[25] Similar mechanisms have been described in vitreoretinal traction.[26] Cuilla et al[27] found that neovascular AMD patients with vitreomacular adhesion and vitreomacular traction needed significantly more intravitreal injections over two years than patients without vitreomacular interface alterations.

A potential limitation of this study may be the use of last generation, low-resolution time-domain-OCT (TD-OCT, Stratus): 30% patients of the RADIANCE study and 8% of our MRS group were followed with TD-OCT. However, previous studies did not find a significant difference in the ability of SD-OCT to detect vitreomacular adhesion and vitreoretinal traction when compared with TD-OCT.[27,28] In addition, all images were carefully analyzed by three independent graders, both facts that should limit the potential bias.

To summarize, MRS is a progressive, degenerative alteration in pathologic myopia and may be found in conjunction with mCNV. Frequent and continuous anti-VEGF treatment effectively control mCNV in eyes with MRS and lead to satisfying treatment results. More intravitreal injections may be needed in these cases to achieve comparable results. Intravitreal interventions may affect the development but rather not the course of existing MRS in high myopic eyes. However, we should be cautious in concluding that there is no significant difference in visual outcome and morphological response in mCNV patients with or without MRS based on our relatively low number of patients. Further studies and observations with larger number of patients and longer term of follow-up are needed.

Key words: pathologic myopia, macular retinoschisis, choroidal neovascularization, ranibizumab.

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