

Anti-vascular endothelial growth factor therapy for the treatment of myopic choroidal neovascularization

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Abstract: Myopic choroidal neovascularization (CNV) is a sight-threatening condition which occurs in eyes with myopia, particularly in those with pathologic myopia. It is the most common cause of CNV among patients younger than 50 years. Hemorrhage and exudation from the CNV lesion may eventually result in scarring or chorioretinal atrophy. While myopic CNV was previously treated with focal laser photocoagulation or photodynamic therapy (PDT), the current treatment of choice is anti-vascular endothelial growth factor (VEGF) agents. Many studies have demonstrated the efficacy of intravitreal anti-VEGF agents in the treatment of myopic CNV. The RADIANCE study reported that intravitreal ranibizumab was superior to PDT in eyes with myopic CNV (at 3 months, both groups receiving intravitreal ranibizumab gained 10.5 and 10.6 letters vs 2.2 letters among patients receiving PDT). In addition, the study demonstrated similar visual outcomes in eyes treated on the basis of visual acuity stabilization or disease activity criteria. Other clinical studies have provided evidence for the efficacy of ranibizumab and aflibercept in the treatment of myopic CNV. This review addresses the epidemiology, pathophysiology, and imaging characteristics of myopic CNV, and discusses the evidence for the efficacy of anti-VEGF agents as compared to laser photocoagulation and PDT.

Keywords: myopic choroidal neovascularization, ranibizumab, anti-vascular endothelial growth factor

Introduction

Myopic choroidal neovascularization (CNV) is a sight-threatening condition associated with myopia, especially high or pathologic myopia. It is characterized by the presence of choroidal neovascularization, which may result in hemorrhage and exudation. Subsequently, the hemorrhage may resolve, leaving a pigmented scar (called a Fuch's spot or Forster Fuch's spot) or chorioretinal atrophy.

Epidemiology of myopic CNV

Myopic CNV is the commonest cause of CNV among patients younger than 50 years.¹ The prevalence of myopic CNV is reported to be 0.05% among patients older than 49 years in the Blue Mountains Eye Study,² and 0.04% among those above 40 in the Beijing Eye Study – both population-based studies.³

Among subgroups with pathologic myopia (estimated to occur among between 5% and 11% of the population), the frequency of myopic CNV was higher: 1.5% in the Beijing Eye Study³ and 6% in the Blue Mountains Eye Study.² The prevalence of myopic CNV also varies with population and demographic characteristics. In a myopia clinic in the United States, 5.2% of patients with axial length >26.5 mm had

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myopic CNV,⁴ whereas this occurred in 11.3% of eyes with either refraction of more than -8D or axial length $>26.5\text{ mm}$ in a high myopia clinic in Japan.⁵

It is important to realize, however, that criteria used to diagnose myopic CNV varies between various studies, and there is no standard definition for myopic CNV. Therefore, any comparison of the prevalence of myopic CNV needs to account for this variation. While myopic CNV was previously believed to occur only in eyes with high myopia (or pathologic myopia), it is now recognized that this condition may occur in eyes with any degree of myopia, as well as in eyes without clinical signs of myopic degeneration.⁶

In a systematic review of myopic CNV, it was reported that myopic CNV occurs more commonly among females, with a prevalence of between 52% and 87.7% among the female population.⁷ Correspondingly, the prevalence among males varied from 12.3% to 48%. It has been postulated that the increased prevalence of myopic CNV among females may be related to the expression of the estrogen receptor in CNV membranes associated with this disease.⁸

Pathophysiology of myopic CNV

While the precise etiology of myopic CNV is yet to be confirmed, several theories have been proposed. The mechanical theory postulates that progressive elongation along the anteroposterior axis, which occurs in myopia, results in stretching of the retina, which may be associated with increased vascular endothelial growth factor (VEGF) production.⁹ In support of this theory, lacquer cracks are often sites of myopic CNV occurrence.¹⁰

The hemodynamic theory suggests that myopic CNV may develop as a result of perfusion changes in the choroid.¹¹ It is known that the choroid thins with increasing severity of myopia,^{12,13} and choroidal thinning has been reported to be more severe among eyes with myopic CNV.^{14,15}

In contrast to mechanical or perfusion-factor changes, the hereditodegenerative theory postulates a genetic predisposition for myopia. Single-nucleotide polymorphisms have been reported to be associated with the development or progression of myopic CNV.^{16,17}

Diagnostic features of myopic CNV

Myopic CNV can be recognized by the presence of a small, grayish-white subretinal membrane on slit-lamp biomicroscopy or color fundus photography.^{6,18,19} This is often associated with an area of subretinal hemorrhage, which may sometimes be masked by the appearance of the surrounding tessellated fundus. If the disease is chronic, there may be pigmented scars or areas of chorioretinal atrophy.^{20,21}

On optical coherence tomography (OCT), myopic CNV manifests as a hyporeflective lesion in the subretinal space (type 2 CNV), often associated with sub- or intraretinal fluid collection.^{19,22} Type 1 CNV (in the sub-retinal pigment epithelium space) is uncommon in myopic eyes.²³

It is also important to assess the choroid in eyes with myopic CNV. Choroidal thickness has been reported to vary among eyes with various retinal diseases.²⁴ In addition, choroidal thickness exhibits significant topographic variation throughout the macula, and also thins as the severity of myopia worsens.^{12,13} Among eyes with myopic CNV, however, the underlying choroid is often thinner compared to normal eyes,^{14,15} and in some cases with severe thinning, may be barely discernible. In a comparison of 23 consecutive patients with bilateral high myopia and unilateral newly developed myopic CNV, the mean subfoveal choroidal thickness was $52\ \mu\text{m}$ among eyes with myopic CNV, compared to $67\ \mu\text{m}$ in the unaffected fellow eye.¹⁴ Similar findings were reported when the choroid was measured superior and inferior to the fovea.¹⁴

Fluorescein angiography (FA) is required to detect leakages from the CNV lesion. The myopic CNV lesion often manifests in a classic pattern of leakage on FA, with early hyperfluorescence that increases in size and intensity in later phases.^{22,25,26} Compared to classic CNV associated with age-related macular degeneration, myopic CNV tends to demonstrate less pronounced leakage,²⁷ which at times can present a challenge when attempting to differentiate fluorescein leakage from staining.

Using fundus autofluorescence, areas of hypo-autofluorescence are seen, corresponding to the myopic CNV lesion, hemorrhage, and regions of chorioretinal atrophy.²⁸

More recently, optical coherence tomography angiography (OCTA) has been used to detect and monitor various retinal diseases,^{29,30} including myopic CNV. Unlike conventional FA and indocyanine green angiography (ICGA), OCTA is noninvasive and does not require the injection of a dye, which avoids potential adverse events due to allergies. In addition, OCTA is able to segment vascular structures from different layers of the retina (superficial and deep capillary plexuses and outer retina) and choriocapillaris, thus facilitating the localization of the lesion. In contrast, FA and ICGA produce a single en-face image with limited amounts of stereopsis. In addition, FA images in the later phases of the angiogram may exhibit leakage from CNV lesions, which may obscure the details of the vessels within it.³¹

Using OCTA, myopic CNV lesions appear as a hyperintense vascular anastomotic network,³² which may appear

circular or irregular in shape.³² The margins of the lesion may appear well-defined or indistinct and a visible core may be detected within the lesion.

Several descriptive terms have been used to describe the myopic CNV lesion.^{33,34}

In some cases, an interlacing network is observed, comprising dense vascular hyperintensity with a well-circumscribed appearance. This lesion has been associated with neovascular activity that is detected by conventional imaging modalities, such as FA and OCT.³² In contrast, a tangled network manifests with a loosely laced appearance, and there is often an absence of neovascular activity on conventional imaging.³²

OCTA has been found to have a sensitivity ranging from 90.5% to 94.1% and a specificity of 93.75% to 100% for identifying CNV.^{32,34} In a study of 26 consecutive patients (22 diagnosed with myopic CNV and four with hemorrhage but no CNV lesion), OCTA detected the presence of a CNV lesion in 16 of 17 eyes (94.1%) where a gradable image was obtained.³⁴ It is important, however, to note that, in some patients, the quality of the OCTA images may not be sufficient to accurately assess the presence or absence of a CNV lesion.³⁴

In addition to detecting the presence of a CNV lesion, OCTA can detect changes in the size and appearance of the CNV lesion following treatment. In addition to a reduction in the overall size of the lesion, changes in vessel density have also been reported.³⁵

Management and treatment of myopic CNV

Previously, myopic CNV was treated using laser photocoagulation or photodynamic therapy (PDT).²⁶ These treatments, however, are associated with complications such as scarring, atrophy, and choroidal ischemia.^{36,37} More recently, anti-VEGF agents have been used in the management of myopic CNV.

Laser photocoagulation

Laser photocoagulation was previously used to treat extrafoveal myopic CNV. However, while there was initial improvement in visual acuity (VA), these gains were not sustained and patients experienced visual loss – due to laser scar expansion which eventually involved the fovea or recurrent CNV.^{38,39}

Recurrent CNV has been reported to occur at the margins of previous laser photocoagulation, suggesting that photo-thermal disruption of the retinal pigment epithelium and

Bruch's membrane may stimulate the development of new CNV lesions in some patients.^{40,41}

Verteporfin photodynamic therapy

PDT has been used to treat myopic CNV because of its ability to facilitate application of the treatment at or near the fovea, with less damage compared to laser photocoagulation.^{42,43} In the Verteporfin in Photodynamic Therapy (VIP) study, it was shown that PDT had a better outcome compared to placebo in study groups over 12 months.^{44,45} These findings are supported by other studies on PDT in myopic CNV.⁶ In addition, PDT may delay further deterioration among patients with myopic CNV.⁴⁶ It is important to note, however, that patients treated with verteporfin photodynamic therapy (vPDT) did not experience an improvement in VA; the treatment served to stabilize the VA, but did not result in improvement. A 2-year follow up of the VIP trial reported no statistically significant benefit in visual outcome when PDT was compared to placebo, although it should be noted that the study may have been underpowered to detect differences in visual outcomes.⁴⁴

In addition, a long-term complication of PDT is the development of chorioretinal atrophy, which may result in visual loss.^{36,37} In a retrospective review of 43 eyes treated with PDT, it was reported that macular chorioretinal atrophy developed in 83% of patients at 5 years.³⁷

Visual loss following PDT may be related to the treatment zone that is selected for application of the PDT treatment spot. In a review of 24 consecutive patients with myopic CNV, 13 were found to have extrafoveal CNV based on FA findings.⁴⁷ The eyes with extrafoveal CNV were subdivided into those with foveal-sparing PDT (where the PDT laser spot did not involve the foveal center) and foveal-involved PDT (where the PDT laser spot included the fovea). Throughout the follow-up period, the group with foveal-sparing PDT had significantly better VA compared to the group where the fovea was covered by the laser. At the final visit, the mean logarithm of the minimal angle of resolution (LogMAR) VA was 0.26 in the foveal-sparing group compared to 1.00 for the foveal-involved group ($p=0.003$). At Month 24, 77.8% of the group with foveal-sparing PDT achieved best-corrected visual acuity (BCVA) $\geq 20/40$, compared to only 25% of those with foveal-involving PDT, and 9.1% with subfoveal CNV lesions ($p=0.006$).⁴⁷

Intravitreal anti-VEGF agents

RADIANCE study

Ranibizumab And PDT [verteporfin] evaluation in myopic Choroidal neovascularization (RADIANCE) was the first

phase III, randomized, double-masked, multicenter, active-controlled trial for myopic CNV.⁴⁸ The study was conducted to evaluate the safety and efficacy of two different dosing regimens of ranibizumab versus vPDT in patients with myopic CNV.

The RADIANCE study enrolled 277 patients with visual impairment due to myopic CNV from 76 centers worldwide, and included both Caucasian and Asian patients. Patients were randomized 2:2:1 to ranibizumab 0.5 mg treatment based on VA stabilization criteria (Group I, n=106), ranibizumab 0.5 mg treatment based on disease activity (Group II, n=116), and vPDT (Group III, n=55).⁴⁸

Patients in Group I received ranibizumab on Day 1, Month 1, and pro re nata (PRN) thereafter, based on VA stabilization criteria. VA stabilization was defined as no change in BCVA as compared to two preceding monthly visits. A minimum of two monthly injections were administered, after which treatment was stopped if VA stabilization criteria were fulfilled. Patients in Group II received ranibizumab 0.5 mg on Day 1. From Month 1, treatment was discontinued if no disease activity was observed. Disease activity included visual impairment attributable to intra- or subretinal fluid collection (seen on OCT) or active leakage secondary to myopic CNV, which was seen on FA. In Group III, patients were treated with verteporfin PDT (standard fluence for 83 seconds) on Day 1. From months 3 to 11, patients in Group III could receive either ranibizumab or additional PDT, or both, based on disease criteria.

The primary objective of RADIANCE was to demonstrate the superiority of ranibizumab over PDT at Month 3. Additional objectives included a non-inferiority assessment between groups I and II at Month 6.

The RADIANCE study reported that ranibizumab treatment (guided by either VA stabilization or disease activity criteria) was superior to verteporfin PDT from baseline to Month 1 through Month 3 (Group I: +10.5 letters, Group II: +10.6 letters, Group III: +2.2 letters; both $p < 0.00001$). In addition, between months 1 and 6, the treatment outcome of patients treated based on disease activity criteria (Group II) was non-inferior to that of the group treated based on VA stabilization criteria (Group I; +11.7 letters vs +11.9 letters, both were statistically significant, $p < 0.0001$).

At Month 12, all three groups gained in BCVA (Group I: +13.8, Group II: +14.4, Group III: +9.3) relative to baseline. It is important to note, however, that patients in Group III were permitted treatment with ranibizumab from Month 3. By Month 12, gain of ≥ 15 letters was observed in 53.3% of Group I, 51.7% of Group II, and 32.7% of Group III

subjects, respectively. Patients in Group I received a median of four injections, compared to two in both groups II and III. In addition, $>60\%$ of those in Group II did not require any additional injections from Month 6 onward.

In both groups I and II, the proportion of CNV leakage decreased significantly between baseline and Month 12 (Group I: 96.2% to 21.0%; Group II: 93.1% to 19.0%). Similar findings were noted when analyzing for the presence of intraretinal edema (Group I: 84.8% to 2.9%; Group II 79.3% to 4.3%).

In addition to improvements in BCVA and improved anatomic findings, patients also demonstrated improvements in quality of life, based on National Eye Institute Visual Function Questionnaire (NEI VFQ)-25 scores, when assessed at months 3 and 12.

REPAIR study

The REPAIR study⁴⁹ was a phase II, prospective, open-label multicenter study of 65 patients with myopic CNV treated with ranibizumab 0.5 mg. At 12 months, patients experienced a gain in mean BCVA of 13.8 letters compared to baseline. Overall, 86% of patients experienced improvement in mean BCVA, with 50.8% achieving a gain of ≥ 10 letters, and 36.9% gaining ≥ 15 letters.

In addition, there was a significant reduction in central macular thickness of 135 μm at Month 12 compared to baseline. Over the course of the study, the proportion of eyes with subretinal fluid decreased from 67.7% to 7.7% ($p < 0.001$, McNemar test), while the proportion with intraretinal cysts decreased from 52.3% to 13.8%, and the proportion with edema from 87.7% to 7.7%.

Other studies on treatment with ranibizumab

Similar to the above results, other studies have reported gains in BCVA in eyes with myopic CNV treated with intravitreal ranibizumab.⁵⁰⁻⁵⁴

Kung et al⁵⁴ conducted a retrospective review of 46 eyes with myopic CNV treated with two different initial dosing regimens: Group 1 (25 eyes) – single intravitreal injection; Group 2 (21 eyes) – three consecutive monthly injections. At Month 12, the mean BCVA was similar in both groups (0.23 vs 0.22), and both groups experienced significant gains in BCVA (0.58–0.23 for Group 1 and 0.55–0.22 for Group 2; both $p < 0.001$; Wilcoxon signed-rank test). The mean number of injections was 2.32 (± 1.22) in Group 1 and 3.57 (± 1.12) in Group 2 ($p = 0.001$; two-tailed t -test), in their study.

Treatment with Aflibercept – MYRROR study

The MYRROR study⁵⁵ was a randomized controlled trial of 122 Asian patients with myopic CNV, who were randomized 3:1 to treatment with intravitreal aflibercept 2 mg (n=91) or sham/intravitreal aflibercept treatment (n=31). Initial treatment was either with intravitreal aflibercept or sham treatment until the primary endpoint at 24 weeks, following which the sham group was switched to aflibercept 2 mg.

At Week 24, patients receiving aflibercept gained a mean of 12.1 letters compared to a loss of 2.0 letters for the sham group (a difference of 14.1 letters, $p < 0.0001$). Following the switch of the sham group to aflibercept after Week 24, patients originally treated with aflibercept from baseline had gained a mean of 13.5 letters by Week 48, whereas the sham group that was switched at Week 24 gained only 3.9 letters ($p < 0.0001$). The proportion of patients gaining ≥ 15 letters at Week 24 was 38.9% in the aflibercept group, compared to 9.7% among those receiving sham treatment ($p = 0.0001$). Even after the sham group was switched to aflibercept, the proportion with ≥ 15 letters at Week 48 was 50.0% in the aflibercept group and 29.0% in the sham/aflibercept group ($p = 0.0001$).

Among patients receiving intravitreal aflibercept from the start, the median number of injections was 2.0 (mean 2.0) in the first quarter and 0 (mean 0.9) in the second quarter. In the third and fourth quarters, this group received a median of 0 injections (mean 0.8 and 0.5 for the third and fourth quarters, respectively). In contrast, from Week 24, the sham/aflibercept group received a median of two injections (mean 1.8) in the third quarter and one injection (mean 1.2) in the fourth quarter.

Conclusion

Myopic CNV is an important condition, especially among populations with a high prevalence of high myopia. Early treatment is beneficial, and current evidence supports the use of intravitreal anti-VEGF agents over laser photocoagulation and/or PDT for the treatment of myopic CNV.

Disclosure

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