

# Anti-VEGF treatment for myopic choroid neovascularization: from molecular characterization to update on clinical application

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**Abstract:** Choroidal neovascularization (CNV) secondary to pathologic myopia has a very high incidence in global, especially in Asian, populations. It is a common cause of irreversible central vision loss, and severely affects the quality of life in the patients with pathologic myopia. The traditional therapeutic modalities for CNV secondary to pathologic myopia include thermal laser photocoagulation, surgical management, transpupillary thermotherapy, and photodynamic therapy with verteporfin. However, the long-term outcomes of these modalities are disappointing. Recently, intravitreal administration of anti-VEGF biological agents, including bevacizumab, ranibizumab, pegaptanib, aflibercept, and conbercept, has demonstrated promising outcomes for this ocular disease. The anti-VEGF regimens are more effective on improving visual acuity, reducing central fundus thickness and central retina thickness than the traditional modalities. These anti-VEGF agents thus hold the potential to become the first-line medicine for treatment of CNV secondary to pathologic myopia. This review follows the trend of “from bench to bedside”, initially discussing the pathogenesis of myopic CNV, delineating the molecular structures and mechanisms of action of the currently available anti-VEGF drugs, and then systematically comparing the up to date clinical applications as well as the efficacy and safety of the anti-VEGF drugs to the CNV secondary to pathologic myopia.

**Keywords:** formation of new vessels, choroid membrane, pathologic myopia, vascular endothelial growth factor, molecular mechanisms, clinical trials

## Introduction

Pathologic myopia is defined as eyes with a refractive error of more than  $-6$  diopters or an axial length of more than 26.5 mm, and with typical pathologic changes at fundus.<sup>1</sup> Choroidal neovascularization (CNV) is the sight-threatening complication occurring in approximately 5.2%–10.2% of highly myopic eyes.<sup>2,3</sup> The CNV secondary to pathologic myopia is one of the most common causes of irreversible central vision loss in the Asian population. It severely deteriorates quality of life and generates huge socioeconomic burdens as it mainly affects the population aged 40 and above.<sup>4</sup> Traditional therapeutic modalities for myopic CNV include laser photocoagulation for extrafoveal and juxtafoveal CNV,<sup>5,6</sup> and verteporfin photodynamic therapy (PDT) for subfoveal CNV.<sup>7,8</sup> Nonetheless, the patients with myopic CNV show variable responses to these modalities<sup>9–16</sup> and have a poor natural history.<sup>17</sup> On the other hand, pilot studies have recently demonstrated the safety and promising efficacy of anti-VEGF therapy in treating CNV secondary to pathologic myopia, and the anti-VEGF agents have been proposed as the first-line therapy for subfoveal and juxtafoveal myopic CNV.<sup>18</sup>

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## Pathogenesis of myopic CNV

Myopic CNV is characterized by the ingrowth of new and fragile blood vessels beneath retinal pigment epithelium (RPE) and/or retina in the myopic eye. The pathogenic mechanisms underlying this disease remain unclear, although, several major contributing factors have been proposed.

First, the mechanical stress caused by progressive and excessive extension of the eyeball along anteroposterior axis results in breaks in the RPE–Bruch's membrane–choriocapillaris complex, a degenerative change termed lacquer cracks.<sup>19</sup> The lacquer cracks induce the molecular and cellular changes in the RPE that promote neovascularization from the choroid capillaries, mimicking the process of wound healing.<sup>1</sup> The high incidence of lacquer cracks accompanying myopic CNV supports this pathogenic mechanism.<sup>20</sup> On the other hand, the *in vitro* studies have shown that mechanical stretch of the RPE cells up-regulates pro-angiogenic factors, such as VEGF.<sup>21</sup> Therefore, excessive distension of the eyeball during pathologic myopia may directly cause RPE stress and imbalanced production of pro-angiogenic factors, eg, VEGF, and anti-angiogenic factors exemplified by PEDF. This imbalance then leads to CNV secondary to pathologic myopia.

Second, genetic susceptibility plays a role in the high refractive errors, the anatomical defects on the coats of eyeball, and the onset and progression of myopic CNV.<sup>22</sup> This notion is supported by the results of familial aggregation and linkage studies,<sup>23</sup> as well as the findings that single nucleotide polymorphisms in the genes encoding CFI,<sup>24</sup> VEGF,<sup>25</sup> and PEDF<sup>26</sup> are associated with occurrence or growth of the CNV secondary to pathologic myopia.

Third, angiographic and anatomical studies of myopic CNV patients demonstrated significant choroidal filling delay<sup>27</sup> and diffuse choroidal thinning,<sup>1</sup> two indicators of

impaired choroidal perfusion. The choroidal circulation provides oxygen and nutrients to the outer retina that contains the most metabolically active photoreceptor cells and is a large source of VEGF production. Thus, the diminished choroidal perfusion may sequentially cause ischemia in the outer retina and RPE, up-regulation of the pro-angiogenic factor VEGF, and development of CNV in pathologic myopia.

Another factor is sex difference. The myopic CNV is far more common in females than males. However, whether this sex variation is due to a more sedate life style or exposure to endogenous and exogenous estrogen remains unknown.<sup>28</sup>

Nonetheless, for individual cases of myopic CNV, these factors may be involved in the pathogenesis in a combinatorial or sequential manner. For example, genetic susceptibility may predetermine the high refractive error and degenerative changes. The mechanical stress resulting from excessive eyeball elongation is more likely to cause choroidal breaks and ischemia, both of which, in turn, can give rise to CNV induced by up-regulated production of VEGF.<sup>1</sup> Therefore, VEGF is the direct trigger of CNV in pathologic myopia, and has become the predominant therapeutic target for this disease. Several anti-VEGF agents with distinctive molecular structures and mechanisms of action have been developed in recent years.

## Molecular characterization of anti-VEGF agents

Bevacizumab (trade name Avastin) is a full-length humanized anti-VEGF monoclonal antibody with a molecular mass of 149 kDa (Table 1). It is composed of 93% structural region of human antibody and 7% complementarity-determining region of murine monoclonal antibody.<sup>29</sup> Bevacizumab binds to all the VEGF isoforms (mainly VEGF-A), antagonizing the binding of VEGF to its cognate receptors, VEGFR-1 and VEGFR-2, on the surface of vascular endothelial cells,

**Table 1** Molecular characterization of anti-VEGF drugs

Name	Molecular weight (kD)	Half-life (day)	Binding specificity	Fc fragment	Structure components
Bevacizumab	149	5.6	VEGF <sup>30</sup>	Humanized IgG	A full-length humanized anti-VEGF monoclonal antibody <sup>29</sup>
Ranibizumab	48	3.2	VEGF-A <sup>35</sup>	No	A humanized monoclonal antibody with only Fab <sup>35</sup>
Pegaptanib	50	10	VEGF-164/165 <sup>37</sup>	Humanized IgG	A pegylated oligonucleotide aptamer <sup>37</sup>
Aflibercept	115	4.8	VEGF-A, VEGF-B, PIGF <sup>40,41</sup>	Human IgG	A chimeric receptor comprised of the 2nd Ig domain of VEGFR-1, the third Ig domain of VEGFR-2 in the Fab, and a human IgG Fc <sup>40,41</sup>
Conbercept	143	5.3	VEGF, PIGF <sup>44</sup>	Human IgG	A chimeric receptor containing the second Ig domain of VEGFR-1, the third and fourth Ig domains of VEGFR-2, and a human IgG Fc <sup>44</sup>

and blocking the signal transductions mediated by VEGF/VEGFRs.<sup>30</sup> Therefore, bevacizumab can inhibit the biological activities of VEGF, including, but not limited to, prevention of the endothelial cells from proliferation, migration, and tube formation, which, in turn, leads to inhibition of neovascularization under pathologic conditions, such as cancer metastasis.<sup>31</sup> Currently, bevacizumab is used as an off-label drug to treat neovascular and exudative ocular diseases,<sup>32,33</sup> but has not been approved in clinical trials.

Ranibizumab (trade name Lucentis) is a recombinant protein with only antigen binding fragment (Fab) of a humanized monoclonal antibody (Table 1). It is the first anti-VEGF protein drug approved by the US Food and Drug Administration (FDA) for ocular disease.<sup>34</sup> The lack of Fc fragment accelerates the entrance of the drug from vitreous cavity to systemic circulation, shortens the half-life, and may mitigate the Fc fragment-associated immune response. Ranibizumab competitively binds to all isoforms of VEGF-A and sequesters them from receptor binding, thereby exerting anti-permeability and anti-angiogenic functions.<sup>35</sup> It has been shown that ranibizumab inhibited vascular permeability in hairless guinea pigs and suppressed the proliferation of human umbilical vein endothelial cells induced by three active forms of VEGF-A, VEGF-110, VEGF-121, and VEGF-165, in a dose-dependent manner.<sup>36</sup> Moreover, ranibizumab has been approved in clinical trials for treatment of CNV secondary to pathologic myopia due to its anti-angiogenic property.

Pegaptanib (trade name Macugen) is a 28-base ribonucleic aptamer, which is a pegylated oligonucleotide with a special three-dimensional conformation that confers specificity and sensitivity to VEGF binding (Table 1). Pegaptanib mainly binds to VEGF-165, one of VEGF-A isoforms, and inhibits the binding of this isoform to VEGFR-2 in vivo (Table 1).<sup>37</sup> Pegaptanib blocks the VEGF-165-mediated intracellular signaling and calcium mobilization, thereby inhibiting pro-angiogenic behavior of endothelial cells, as well as vascular leakage and neovascularization at the tissue level.<sup>38,39</sup>

Aflibercept (trade name VEGF Trap-eye [VTE] or EYLEA) contains the second Ig-like domain of VEGFR-1 and the third Ig-like domain of VEGFR-2 in its Fab fragment, and it has high affinity to all isomers of VEGF-A, VEGF-B and PGF.<sup>40,41</sup> By fusing the Fab fragment with an IgG Fc backbone of human origin, aflibercept forms a chimeric protein with higher affinity to VEGF isomers and longer intravitreal half-life than bevacizumab.<sup>42,43</sup> Given the molecular properties of aflibercept, the regimen with less intravitreal injections (one injection in every 2 months) was performed in clinical trials, and similar efficacy and safety outcomes were achieved in

patients with wet age-related macular degeneration (wAMD) as compared to the monthly injection regimen.<sup>43</sup>

Conbercept is a recombinant fusion protein containing the second Ig-like domain of VEGFR-1, the third and fourth Ig-like domains of VEGFR-2, as well as an Fc fragment of human IgG. Conbercept differs from aflibercept by adding the fourth Ig-like domain of VEGFR-2 in the Fab fragment.<sup>44</sup> Conbercept consequently has a higher affinity to VEGF, because the fourth domain of VEGFR-2 is essential for the receptor dimerization and enhances the association rate of VEGF to the receptor.<sup>44</sup> Conbercept inhibits the VEGF-induced proliferation of human umbilical vein endothelial cells, and intravitreal injection of conbercept significantly ameliorated the laser-induced CNV and vascular leakage in the eyes of rhesus monkeys.<sup>45</sup>

## Clinical applications of anti-VEGF drugs

### Bevacizumab

Bevacizumab is one of the first FDA-approved drugs for inhibition of tumor angiogenesis. Although it has not been officially approved in clinical trials, a number of studies around the world have reported the efficacy outcomes of intravitreal bevacizumab (IVB) injection for myopia-associated CNV following variable time periods.

In a short-term prospective interventional study in Mexico, Hernández-Rojas et al<sup>46</sup> performed an intravitreal injection of 2.5 mg bevacizumab on myopic CNV patients, and the patients were followed-up for 3 months. The visual acuity (VA) was significantly improved from 20/200 to 20/100 at 2 weeks following the injection, to 20/80 at 4 weeks, and to 20/60 at 8 and 12 weeks after the treatment. The average foveal thickness in these patients was  $(385.43 \pm 125.83)$   $\mu\text{m}$  before the treatment, and was reduced to  $(257.64 \pm 76.6)$   $\mu\text{m}$  at the first month and to  $(194.54 \pm 54.35)$   $\mu\text{m}$  at the third month post injection (Table 2). In another study conducted in Hong Kong, People's Republic of China, the patients with myopic CNV received three monthly injections of 1.25 mg bevacizumab.<sup>47</sup> At the first and sixth month following the first injection, the mean logarithm of the minimum angle of resolution (logMAR) of the best-corrected visual acuity (BCVA) improved significantly to 0.43 and 0.35; the mean VA improved 1.7 and 2.6 lines, respectively. The VA of 68.2% cases had improved two or more lines at the completion of the study (6 months following the initial injection). Anatomically, optical coherence tomography (OCT) revealed a significant reduction in central foveal thickness (CFT) after treatment (Table 2).<sup>47</sup> A similar study was also

**Table 2** Comparison of therapeutic effects of anti-VEGF drugs for myopic CNV

Parameters	Bevacizumab	Ranibizumab	Pegaptanib	Aflibercept
BCVA	At 6 m: $\geq 2$ lines <sup>46</sup> At 12 m: $\geq 10$ letters <sup>47</sup> At 24 m: $\geq 3$ lines <sup>48</sup>	At 8 m: 3 lines <sup>59</sup> At 12 m: 3 lines <sup>60</sup> NA	NA At 12 m: 10 letters <sup>67</sup> NA	At 6 m: 12.1 letters <sup>70</sup> At 12 m: 13.5 letters <sup>70</sup> NA
CFT	At 6 m: decreased from 251 to 206 $\mu\text{m}$ <sup>61</sup> At 12 m: decreased from 223 to 206 $\mu\text{m}$ <sup>47</sup> At 24 m: decreased from 313 to 254 $\mu\text{m}$ <sup>48</sup>	At 6 m: decreased from 237 to 185 $\mu\text{m}$ <sup>61</sup> NA NA	At 12 m: decreased 20% <sup>67</sup> NA NA	NA NA NA
CRT	NA NA	At 6 m: decreased from 109.3 to 103.4 $\mu\text{m}$ <sup>58</sup> At 12 m: decreased from 166.6 to 161.1 $\mu\text{m}$ <sup>58</sup>	NA NA	Parallel reduction <sup>70</sup> NA
Retinal sensitivity	NA	NA	At 12 m: improved from 7.48 to 8.15 dB <sup>66</sup>	NA
Maximum lesion diameter	NA	NA	At 12 m: reduced from 1,217 to 1,041 $\mu\text{m}$ <sup>66</sup>	NA
Metamorphopsia	At 12 m: completely disappeared in 87.5% of the treated eyes <sup>82</sup>	NA	At 12 months: scores changed from 0.85 to 0.50 <sup>66</sup>	NA
Microperimetry	NA	NA	At 12 months: increased from 8.40 to 10.80 dB <sup>67</sup>	NA

**Abbreviations:** CNV, choroidal neovascularization; BCVA, best-corrected visual acuity; CFT, central fundus thickness; CRT, central retina thickness; m, months; NA, not available.

reported from Italy except that the patients were followed-up for 12 months after three monthly IVB injections, the BCVA improved more than ten letters in 90% of patients, and more than 15 letters in 70% of them. The mean CFT decreased from (223 $\pm$ 47.43)  $\mu\text{m}$  at the baseline to (206 $\pm$ 50.87)  $\mu\text{m}$  at the end of the follow-up, however, this change did not reach statistical significance (Table 2).<sup>48</sup> When the follow-up was extended to 24 months in a more recent study in Italy, the mean logMAR BCVA of the myopic patients with CNV was improved from 0.47 (20/60 on Snellen chart) to 0.22 (20/30 on Snellen chart), and 46.6% eyes achieved the improvement of at least three Early Treatment of Diabetic Retinopathy Study (ETDRS) lines. The mean central macular thickness was significantly decreased from 313 to 254  $\mu\text{m}$ , and the mean CNV size reduced from 348 to 251  $\mu\text{m}^2$ .<sup>49</sup> Voykov et al<sup>50</sup> obtained similar results in a study conducted in Germany. More impressively, after 4 years of follow-up in a retrospective study, the VA of 71.4% of the eyes was improved more than one line on Snellen chart.<sup>51</sup> The results of these studies suggest the considerable efficacy of IVB in treating myopic CNV in global populations.

In order to optimize the IVB therapeutic regimen, Wakabayashi et al<sup>52</sup> examined the VA and the re-treatment rate following single injection or three monthly injections of IVB for myopic CNV. BCVA in both groups was significantly

improved as compared to the prior injection level at 3, 6, and 12 months after the first injection. However, no significant difference was found between the groups in mean logMAR BCVA, recurrence rate, and persistence of CNV. The results demonstrated that, in comparison to the three monthly injections followed by treatment as needed, single IVB plus the treatment as needed requires fewer injections but generates similar VA outcomes for at least 12 months.

Furthermore, the treatment efficacy of IVB for myopic CNV was compared to the traditional modalities. For example, Ikuno et al<sup>53</sup> compared the effects of PDT with verteporfin and IVB in Japanese women with myopic CNV. The BCVA of the PDT group did not show any significant improvement during the first year, and started to deteriorate thereafter, especially between 18 and 24 months following the treatment, with the BCVA being significantly inferior to the level before the treatment. These results are consistent with those observed in another 2-year study, where Parodi et al<sup>54</sup> compared the effects of laser treatment (LT) and PDT to those of IVB in Italian patients with juxtafoveal myopic CNV. At the end of the 2-year follow-up, the mean VA of the PDT group decreased, whereas that of the LT group did not significantly differ from the baseline level; in contrast, the VA of the IVB group in both studies improved significantly with time. In another study, the effects of IVB were compared

with those of sub-Tenon injection of triamcinolone acetonide (sub-Tenon TA), a synthetic corticosteroid administered ectopically to treat ocular neovascularization and diabetic edema.<sup>55</sup> At 12 months following the initial injection, the BCVA of IVB group improved 1.9 lines; whereas that of sub-Tenon TA group dropped 0.3 lines.<sup>56</sup> Taken together, these results suggest that IVB generates VA outcomes greatly superior to the traditional therapeutic modalities.

Overall, the IVB-treated eyes demonstrated significantly improved BCVA and diminished retinal foveal thickness in OCT examination, bevacizumab hence provides better functional and anatomical outcomes than the traditional modalities for treating myopic CNV, although its Fc fragment of rodent origin might increase the risk of immune response and the occurrence of endophthalmitis.

## Ranibizumab

Ranibizumab is a recombinant protein that only contains the Fab fragment of a humanized monoclonal antibody to VEGF-A, thereby potentially accelerating its clearance from the target tissue and reducing the risk of immune response. It is designed for ocular administration, and has been approved by the FDA for the treatment of wAMD since 2006.<sup>57</sup> Ranibizumab has recently been used to treat CNV secondary to pathologic myopia.

In a Phase I clinical trial conducted by Heier et al<sup>58</sup> the effects of intravitreal ranibizumab (IVR) injection were studied in patients with CNV secondary to causes other than wAMD. Six months after treatment, 66.7% of the patients gained more than 15 letters of VA. The mean central retinal thickness decreased significantly from baseline at both 6 and 12 months following the initial IVR, suggesting efficacy and safety of IVR in CNV caused by diseases other than wAMD (Table 2). Besides, Ouhadj et al<sup>59</sup> performed IVR in patients with subfoveal or juxtafoveal CNV secondary to pathologic myopia and followed-up with them for an average of 8 months. All patients maintained or improved their vision, and the average increase of VA was three lines (range: 1–9 lines) (Table 2). In another study, myopic CNV patients received three monthly injections of IVR and were followed-up for 12 months. At 12 months post treatment, the mean improvement of VA was 3.0 lines, and 75.0% eyes had two or more lines of improvement; whereas OCT showed a significant reduction in the mean foveal thickness (Table 2).<sup>60</sup>

A large number of literature have reported the safety and efficacy of both bevacizumab and ranibizumab in the treatment of CNV secondary to pathologic myopia, but then

which anti-VEGF agent would be more efficacious and cost-effective in treating this ocular disorder? To answer this question, several studies compared the effects of IVB and IVR on myopic CNV at 6 months (Table 2),<sup>61</sup> 2 years,<sup>62</sup> and 4 years<sup>63</sup> after initial treatment. The results showed that the BCVA improvement and CFT reduction were all similar between the two treatment groups at each time point examined. In the study conducted by Iacono et al<sup>64</sup> the BCVA and central macular thickness were not significantly different between IVB and IVR group at the end of the 18-month follow-up. However, the IVR group achieved a faster central macular thickness reduction and required less injections than the IVB counterpart, implicating the greater efficacy of ranibizumab in treating myopic CNV.

## Pegaptanib sodium

Pegaptanib sodium, as one of the first-class therapeutic agents targeting pathogenic mechanisms of wAMD, was approved for treatment of this disease by the FDA in 2004.<sup>65</sup> Pegaptanib sodium has also been applied in the treatment of CNV secondary to pathologic myopia within the last 3 years.

Kitagawa and Yuzawa<sup>66</sup> evaluated the ophthalmologic outcomes resulting from 1-year administration of intravitreal pegaptanib sodium (IVP) in patients with CNV secondary to pathologic myopia. The mean logMAR VA and retinal sensitivity did not change significantly prior to and after the treatment. The mean maximum lesion diameter was significantly reduced from 1,217 to 1,041  $\mu\text{m}$ . Mean metamorphopsia scores were significantly improved both vertically and horizontally (Table 2). Moreover, Rinaldi et al<sup>67</sup> reported a 20% reduction in foveal thickness in myopic CNV after IVP treatment for 48 weeks. In the meanwhile, neovascularization was subdued in all patients with significant improvement in visual functions, including BCVA and microperimetry (Table 2).

More notably, Bennett and Yee<sup>68</sup> reported that a young female patient with myopic CNV who had been refractive to laser photocoagulation, PDT, and intravitreal TA, and was treated with IVP injections for 5 weeks, had ETDRS VA improvement from counting fingers to 20/40 in the right eye. The results suggest that, at least in this case, IVP appears to be more effective than the traditional modalities, including laser, photodynamic, and corticosteroid therapy, for treatment of intractable CNV secondary to pathologic myopia.

## Aflibercept

The effects of aflibercept on the CNV caused by wAMD have been recognized in clinical trials, and it was approved by the

FDA for wAMD in 2011.<sup>69</sup> However, reports on aflibercept treatment for myopic CNV have been relatively scarce except for the results of an international, multi-centered, Phase III clinical trial which were published in March 2015.<sup>70</sup> At 24 weeks following an intravitreal aflibercept (IVA) injection, the BCVA was improved 12.1 letters with a parallel reduction in CFT; whereas the patients who received a sham injection lost two letters of BCVA. The BCVA of the patients receiving IVA continued to improve until 48 weeks after the injection (Table 2).<sup>70</sup> The functional and anatomical benefits following IVA in this study support the addition of aflibercept to the list of therapeutic modalities for myopic CNV.

## Conbercept

Conbercept is a recombinant anti-VEGF fusion protein that was recently engineered by a pharmaceutical company in Sichuan, People's Republic of China. By incorporating three Ig-like domains of VEGF receptors into its Fab fragment, conbercept has high affinity to both VEGF and PlGF. This new generation of anti-VEGF agent was approved by the State Food and Drug Administration in the People's Republic of China for the treatment of wAMD in 2013.<sup>71</sup> Although the clinical trials employing conbercept to treat myopic CNV have not been reported, the effects of this anti-VEGF drug on laser-induced CNV in the non-human primate model are promising. Zhang et al<sup>45</sup> found that conbercept inhibited the VEGF-induced proliferation of human umbilical vein endothelial cells in a dose-dependent manner. Intravitreal injection of high dose conbercept (300, 500 µg) significantly reduced the neovascular leakage examined by fluorescence fundus angiography and OCT, and prevented the formation of fibrovascular membranes revealed by tissue staining. More importantly, multi-focal ERG showed the improvement of visual function after administration of the high dosage conbercept. In a cohort study, the same research group demonstrated a significant improvement in the leakage of laser-induced CNV after the monkeys of the control group were switched to the conbercept treatment group, suggesting the therapeutic effects of conbercept on the pre-existing laser-induced CNV in the animals.<sup>72</sup>

## Potential adverse effects

As with any general intraocular operation, intravitreal injection of anti-VEGF agent comes with the risks of infection, bleeding, glaucoma, and cataracts.<sup>73</sup> The risk of retinal damage post intravitreal injections is increased in myopic eyes, where degenerative changes at the posterior segment

may have already existed.<sup>1</sup> Comprehensive ophthalmic tests should therefore be performed in myopic patients prior to intravitreal injections.

The intravitreal administration of bevacizumab as an off-label drug for wAMD incurs a higher risk of hypertension,<sup>74</sup> atherothrombosis,<sup>75</sup> and stroke<sup>76</sup> than ranibizumab. In addition, the Fc fragment renders bevacizumab a longer half-life and makes it more prone to autoimmunity; re-packaging this drug for ocular use increases the risk of microbial contamination. Indeed, intravitreal injections of bevacizumab have been associated with sterile and non-sterile endophthalmitis.<sup>22</sup> On the other hand, ranibizumab, the anti-VEGF agent originally designed and approved for ocular use, has shown similar efficacy but superior safety profiling to bevacizumab, hence, should be the first choice for myopic CNV treatment, albeit at a higher cost. However, the long-term efficacy and safety of ranibizumab in myopic CNV treatment await further investigations.<sup>77</sup>

VEGF is a trophic factor for both neural retina and retinal vessels,<sup>78</sup> applications of anti-VEGF agents in animal models result in apoptosis of retinal neurons,<sup>79</sup> mitochondrial disruption in photoreceptors,<sup>80</sup> and fenestration reduction in choriocapillaris endothelial cells.<sup>81</sup> Because chorioretinal atrophy develops as a natural history of myopic CNV,<sup>1</sup> whether anti-VEGF may exacerbate chorioretinal atrophy in myopic CNV patients needs to be cautiously monitored.

## Conclusion

Based on the results of clinical studies and trials, the anti-VEGF drugs have demonstrated superior efficacy to the traditional modalities, including PDT, LT, and injection of TA, in the treatment of CNV secondary to pathologic myopia. Therefore, intravitreal injection of anti-VEGF drugs has been proposed as the first-line treatment of CNV secondary to pathologic myopia.<sup>18</sup> Among the anti-VEGF drugs, bevacizumab and ranibizumab exhibit similar efficacy in restoring functional and anatomical parameters. However, ranibizumab is designed and approved specifically for ocular administration, and achieves efficacy with shortened duration, frequency, and adverse effects, hence appears to be the first choice for treatment of myopic CNV when available. Aflibercept and conbercept are the chimeric proteins containing the fragments of murine Fab and human Fc, and belong to the new generation of anti-VEGF agents. They were originally approved for treatment of wAMD, their safety and efficacy in the treatment of myopic CNV need to be confirmed/proven by large-scale rigorous clinical trials.

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## Disclosure

The authors report no conflicts of interest in this work.

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