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MINI-REVIEW ARTICLE

Anti-VEGF Therapy in Myopic CNV

Lisa Toto[1,*], Luca Di Antonio[1], Olivia Costantino[1] and Rodolfo Mastropasqua[2]

[1]*Ophthalmology Clinic, Department of Medicine and Science of Ageing, University G. D'Annunzio Chieti-Pescara, Chieti, via dei Vestini 31, 66100, Italy;* [2]*Institute of Ophthalmology, University of Modena and Reggio Emilia, Modena, Italy*

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Abstract: In this narrative-review, we report the most recent data from the literature of anti-vascular endothelial growth factor treatment for myopic choroidal neovascularization (mCNV). Myopic CNV is the most frequent sight-threatening complication of pathologic myopia. The natural course of mCNV can result in expanding macular atrophy and /or fibrosis, leading to irreversible visual loss after 5 years. Retinal multimodal imaging is mandatory for early diagnosis and monitoring of the disease during treatment. Intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy is recommended as the first-line treatment option for mCNV. Prompt treatment of active mCNV with intravitreal anti-VEGF therapy has been demonstrated to be effective in terms of visual outcome improvements reducing the occurrence of late-stage complications.

Keywords: Myopic choroidal neovascularization, anti-vascular endothelial growth factor therapy, pathologic myopia, fundus fluorescein angiography, bevacizumab, ranibizumab, aflibercept.

1. INTRODUCTION

Myopic choroidal neovascularization (mCNV) is the most frequent sight-threatening complication of pathological myopia (PM), also known as degenerative myopia, a condition characterized by an axial length >26 mm and a refractive error of at least -6.0 diopters (D), often with fundus degenerative changes [1].

Typical features of PM are the presence of myopic maculopathy and/or posterior staphyloma. Myopic maculopathy alterations have been classified into five categories based on fundus photos mainly related to the absence or presence of chorioretinal atrophy of different severity (0-4; META-PM classification) (Table **1**) with possible three additional features as a plus sign that include mCNV, lacquer cracks, and Fuchs' spots [2].

The presence of lacquer cracks has been associated with a higher risk of mCNV development [3].

Table 1. Classification of myopic maculopathy.

	Myopic Maculopathy	"Plus" Lesions
Category 0	No macular lesions	Lacquer cracks
Category 1	Tessellated fundus	
Category 2	Diffuse chorioretinal atrophy	Choroidal neovscularization
Category 3	Patchy chorioretinal atrophy	Fuchs' spot
Category 4	Macular atrophy	

*Address correspondence to this author at the Ophthalmology Clinic, Department of Medicine and Science of Ageing, University G. D'Annunzio Chieti-Pescara, Chieti, via dei Vestini 31, 66100, Italy;
Tel: +39 0871358410; Fax: +39 087135794; E-mail: l.toto@unich.it

The incidence of mCNV ranges between 5%-11% of patients with PM and 0.04%-0.05% of the general population. [4] In patients with pre-existing mCNV, the occurrence of CNV in the fellow eye has been reported in 35% of patients with a mean period of 8 years [4].

The major cause of the permanent visual loss during the natural course of mCNV is macular atrophy and/or fibrosis with a best-corrected visual acuity of 20/200 or less in 88.9% of PM patients after 5 years and of 96.3% in 10 years [5-7].

Retinal multimodal imaging allows detailed diagnosis and disease activity assessment of mCNV (Fig. **1**).

Fundus fluorescein angiography (FFA) with dye injection is considered the gold standard for mCNV detection and evaluation of lesion activity, showing well-defined hyperfluorescence in the early phase with leakage in the late phase in a classic CNV pattern of leakage [8].

At spectral domain optical coherence tomography (S-D-OCT) mCNV appears as a hyper-reflective area above the RPE, usually with minimal subretinal fluid. SDOCT shows high sensitivity (about 97%) in detecting mCNV with less capability in highlighting exudative features compared to FFA [9]. Some features such as the presence of subretinal hyperreflective exudation or the fuzzy borders of CNV causing reduced visibility of external limiting membrane (ELM) have been suggested as signs of mCNV activity at SD-OCT [10, 11].

In the recent years, a new dyeless method called optical coherence tomography angiography (OCTA), has been introduced into daily clinical practice. The OCTA gives more insight deep into the retinal and choroidal microcirculation by revealing flow features of CNV such as shape, size, location and perfusion density [12].

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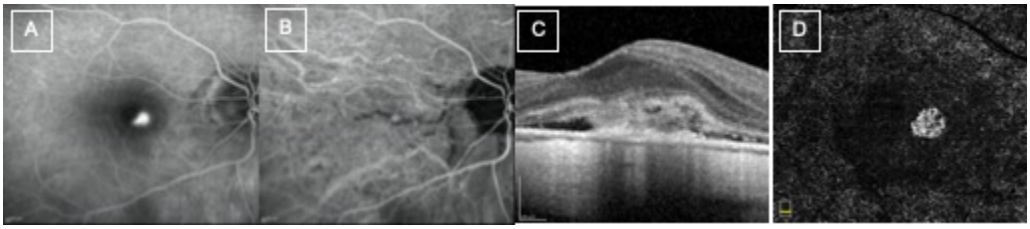

Fig. (1). Multimodal imaging of myopic choroidal neovascularization in pathologic myopia. (**A**) Late phase fluorescein angiography. (**B**) Indocyanine green angiography. (**C**) Spectral domain optical coherence tomography. (**D**) Optical coherence tomography angiography. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

OCTA is capable of highlighting mCNV as a hyperintense vascular anastomotic network with greater detail compared to FFA, due to the absence of masking related to dye leakage [13].

OCTA has a sensitivity ranging from 90.48% to 94.1% in detecting mCNV, with greater difficulty in evidencing small mCNV (<0.01 mm2) [14, 15].

The recent introduction of swept-source OCTA (SS-OCTA) with longer wavelength and a higher scan rate compared with SD OCTA has the potential for more detailed visualization of mCNV in the presence of subretinal fluid and exudative material [16].

Nevertheless, OCTA does not reflect the level of activity of mCNV and shows a neovascular pattern with blood flow even in the presence of fibrosis, occurring after natural evolution or secondary to mCNV treatment [17].

Laser photocoagulation has been used for non-subfoveal mCNV, but with time there is an expansion of the laser-induced atrophy [18, 19].

showed Photodynamic therapy with verteporfin ~~has shown~~ limited efficacy in subfoveal CNV compared with sham treatment [20].

Nowadays, the first-line therapy for mCNV is the intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF), showing efficacy and safety [21].

2. ANTI-VEGF THERAPY FOR mCNV

2.1. Rationale of Anti-VEGF Treatment

Several studies showed the role of several molecules in the pathogenesis of ocular neovascular conditions [22, 23].

Vascular endothelial growth factor (VEGF) is considered the most important regulator of ocular angiogenesis; VEGF causes induction of endothelial cell migration and proliferation after hypoxia. The vascular endothelial growth factor sub-family includes five members (VEGF-A; -B; -C and -D; and placental growth factor, PlGF); among these VEGF-A is considered an important factor in ocular angiogenesis. However, other members of the VEGF family have been found to act on ocular angiogenesis [23].

Myopic CNV is associated with increased levels of VEGF. The up-regulation of VEGF expression is hypothesized to ~~originate~~ derive from RPE and glial cells secondary to hypoxia related to loss of choroidal vessels and/or capillaries occurring in PM [24].

Nowadays, important anti-VEGF drugs used to treat retinal and choroidal angiogenesis include bevacizumab, ranibizumab, aflibercept, ziv-aflibercept and conbercept. Ranibizumab and aflibercept are currently the two main drugs used in mCNV treatment, extensively investigated in clinical trial. Bevacizumab has been evaluated mostly in clinical case series with off-label use of the drug.

Recent evidence of a new anti VEGF molecule such as conbercept in mCNV have shown promising results.

2.2. Ranibizumab Studies

Ranibizumab is a recombinant, humanized, affinity-matured, monoclonal antibody Fab fragment that binds to all isoforms of VEGF-A.

The early ranibizumab studies demonstrated the superiority of intravitreal therapy compared to PDT without differences between different dosing regimens [25-27].

No differences were observed in terms of treatment efficacy when comparing a single injection and a loading dose of 3 injections followed by a PRN regimen [28].

2.2.1. Randomized Clinical Trials

The RADIANCE study, a 12-month, phase III, randomized, double-masked, multicenter clinical trial was the first study on ranibizumab that compared intravitreal ranibizumab (0.5 mg) with verteporfin photodynamic therapy (vPDT) for mCNV. Patients with visual impairment due to active mCNV were randomized to receive ranibizumab on day 1, month 1, and thereafter as needed and guided by VA stabilization criteria (group I, n = 106); ranibizumab on day 1 and thereafter as needed ~~and~~ , guided by disease activity criteria (group II, n=116); or vPDT on day 1 and disease activity treated with ranibizumab or vPDT at investigators' discretion from month 3 (group III, n = 55).

Retreatment was based on either VA stabilization criteria (defined as no change in BCVA

since the two preceding monthly visits) or disease activity criteria (defined as vision impairment, attributable to intra- or subretinal fluid or active leakage secondary to patho-

logic myopia as assessed by OCT and/or FFA). Patients aged ≥18 years with BCVA ≥24 letters and ≤78 letters were eligible for inclusion.

Ranibizumab treatment in groups I and II was superior to vPDT with a mean BCVA increase from baseline to month 3 (group I: +10.5, group II: +10.6 *vs*. group III: +2.2 letters; both P<0.0001). Ranibizumab treatment guided by disease activity was noninferior to VA stabilization-guided retreatment with a mean BCVA change from baseline to month 6 (group II: +11.7 *vs*. group I: +11.9 ETDRS letters; P<0.00001). Patients received a median of 4.0 (group I) and 2.0 (groups II and III) ranibizumab injections over 12 months [25].

In the post-RADIANCE study, forty-one patients who completed the RADIANCE trial were followed-up for up to 48 months. Patients were categorized into 2 post-RADIANCE treatment groups: Group A, those who required additional anti-VEGF during the post-RADIANCE observation period and Group B, those who required no further treatment.

Mean visual gain from baseline BCVA) was significant at 12 months (+14.3 ± 11.4 letters, n = 40, P, 0.0001), 24 months (+10.4 ± 22.3 letters, n = 31, P = 0.0143), 30 months (+11.0 ± 22.4 letters, n = 29, P = 0.0134), 42 months (+12.9 ± 20.9 letters, n = 25, P = 0.0051), and 48 months (+16.3 ± 18.7, n = 16, P = 0.0034). Over the post-RADIANCE observation period, 83% of patients required no further treatment for mCNV, 10% experienced mCNV recurrences requiring a mean of 5.0 (SD 5.9, range 1.0-18.0) ranibizumab injections [26].

BRILLIANCE study was a 12-month, phase III, randomized, double masked, active-controlled study comparing the efficacy and safety of two dosing regimens of ranibizumab 0.5 mg *versus* verteporfin photodynamic therapy in Asian patients with visual impairment due to mCNV [27]. Eligible patients (aged >18 years) were randomized 2:2:1 to Group I (n = 182; ranibizumab treatment guided by visual acuity stabilization criteria); Group II (n = 184; ranibizumab treatment guided by disease activity); or Group III (n = 91; verteporfin photo- dynamic therapy on Day 1; from Month 3, ranibizumab/verteporfin photodynamic therapy/ both treatment guided by disease activity). The mean BCVA change from baseline to month 1 through month 3 was significantly higher in Groups I/II *versus* Group III (Group I/II: +9.5/ +9.8 letters *vs*. Group III: +4.5 letters; both P, 0.001). Group II was statistically noninferior to Group I for the mean BCVA change from baseline to month 1 through month 6 (Group II,10.7 *vs*. Group I, 10.4 letters; P<0.001). The improvements in BCVA were maintained through to 12 months, and no new safety concerns were identified. Over 12 months, the mean number of ranibizumab injections received by Groups I/II/III was 4.6/3.9/3.2.

The SMILE study was a prospective single-blind randomized clinical trial that evaluated and compared the 12--month anatomical, functional outcomes, retreatment and recurrence rate of the two different initial regimens of intravitreal ranibizumab for mCNV treatment consisting of 1+PRN or 3 +PRN ranibizumab treatments based on VA and specific disease activity criteria. At month 12, the mean gain in BCVA was 13.0±10.1 letters in the 1 + prn group, compared with 16.4 ± 9.7 letters gained in the 3 + prn group (P = 0.23). There was no statistically significant difference in BCVA, BCVA changes or proportion of patients gaining 15 letters or more at all measured time points between the two groups. The risk factors for retreatment included 1 + PRN ranibizumab treatment, female, older age and central retinal thickness (CRT) > 300 μm [28].

2.2.2. Prospective Clinical Trials

The REPAIR study was a phase II, prospective, multicenter, single arm 12-month study, study of intravitreal ranibizumab in active primary or recurrent subfoveal or juxtafoveal mCNV. After the initial injection, patients were retreated with a PRN dosing regimen based on BCVA, OCT and FA findings. The primary outcome in terms of mean change in BCVA score was 13.8 letters at 12 months from a baseline level of 59.5 letters (P < 0.001). The greatest improvement was observed in the first month of treatment (mean change, +8.7 letters overall), 86% of patients showed improvement in mean BCVA score, with 24 patients (36.9%) achieving a BCVA gain of ≥15 letters, and 50.8% of patients achieving a gain of ≥10 letters. The mean number of injections was only 3.6 over 12 months [29].

A prospective interventional, non-randomized 12-month study assessed the efficacy of Intravitreal ranibizumab administered in a pro-re-nata regimen with re-treatment based on OCT and FA findings and VA assessment in 48 patients with mCNV. The mean BCVA improved from 0.49 ± 0.30 logMAR to 0.39 ± 0.32 logMAR at 1-year follow-up (P = 0.043). Patients with better baseline BCVA, early diagnosis, lower CMT, or disclosing a fundus hyper autofluorescence CNV pattern achieved better visual outcomes. Patients treated with one to two intravitreal injections (45.8%) obtained better VA compared with patients receiving 3 or more injections [30].

The OLIMPIC study, a prospective, 12-month, phase II-Ib, open- label, interventional, multicenter study evaluated efficacy, safety, and tolerability of ranibizumab with visual impairment due to mCNV. After the initial injection, patients were retreated with a PRN dosing regime- based disease activity, based on functional and/or anatomical features. The mean (SD) BCVA gain from baseline to month 12 was 8.4 ±12.8 letters (P < 0.0001). The mean (SD) number of injections was 2.41 (1.53); range 1-9 [31].

2.2.3. Retrospective Studies

Kung *et al*. conducted a retrospective study in 46 mCNV eyes treated with two different initial dosing regimens: Group 1 (25 eyes) treated with single intravitreal injection; Group 2 (21 eyes) with 3 consecutive monthly injections. At Month 12, the mean BCVA was not significantly different between the two groups, and both groups showed significant gains in BCVA (from 0.58 to 0.23 logMAR for Group 1 and

from 0.55 to 0.22 logMAR for Group 2; both p,0.001). The mean number of injections was 2.32 (±1.22) in Group 1 and 3.57 (±1.12) in Group 2 (p=0.001;) [32].

A retrospective study assessed 6-year VA outcome of ranibizumab therapy in 15 eyes affected by mCNV treated with 1 first injection and retreatment on a PRN regimen based on OCT and FA findings and VA. Baseline VA was 0.65 ± 0.28 logMAR, improved to 0.35 ± 0.24 (p = 0.001) after 1 year, and to 0.39 ± 0.26 (p = 0.016) after 6 years showing that the initial gain was maintained by a strict PRN regimen. Patients received a mean of 3.5 ranibizumab injections (SD 3.4; range 1-12) during a mean follow-up of 85 months (SD 6.6; range 76-102 months) [33].

conducted Onishi *et al*. ~~presented~~ a retrospective 5-year-follow up study on 51 eyes affected by mCNV. At the baseline and at the 1-year, 2-year, 4-year, and 5-year period, the mean BCVAs were 0.38 logMAR units (20/49), 0.27 logMAR units (20/37), 0.31 logMAR units (20/41), 0.35 (20/45) logMAR, and 0.32 logMAR units (20/ 42), respectively. The BCVA was significantly better than the baseline BCVA at 1 year (P = 0.007), but not at 2 (P = 0.15), 4 (P = 0.88), or 5 years (P = 0.89).

The mean number of intravitreal injections of ranibizumab was 1.6, and 34 eyes (66.7%) had only a single intravitreal injection. The BCVA at 5-year period was significantly correlated with the baseline BCVA, the number of IVR injections, and the size of the CNV-related macular atrophy [34] Table **2**.

2.3. Aflibercept Studies

constitutes Aflibercept is a recombinant fusion protein that ~~forms~~ a VEGF trap (binds to both sides of the VEGF-A and -B dimer), also binding to placental growth factor (PlGF).[22]

Randomized clinical trials, prospective and retrospective studies on aflibercept showed similar result to ranibizumab studies confirming the efficacy of PRN regimen with an initial intravitreal injection followed by intravitreal aflibercept injection based on disease activity [35-38].

2.3.1. Randomized Clinical Trials

The MYRROR study, a randomized, controlled clinical trial, evaluated intravitreal aflibercept in 91 patients with myopic CNV *versus* a sham control group of 31 patients.

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.

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 (p,0.0001). Following the switch of the sham group to aflibercept after week 24, patients originally treated with aflibercept from baseline 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). 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 [35].

2.3.2. Prospective Studies

A prospective 12-month cohort study of 31 eyes of 30 consecutive patients affected by CNV associated with PM evaluated the efficacy of intravitreal aflibercept (2 mg) administered with 2 initial monthly doses followed by a PRN regimen based on OCT or fundus examination disease activity criteria. Compared with baseline, BCVA improved significantly at all time points ($P<0.05$) and was 0.2 ± 0.1 at baseline and 0.35±0.16 at month 12. The greatest improvement in BCVA was seen within the first 2 months (P=0.01). Patients received a mean of 2.6 intravitreal aflibercept injections over the 12-month study period [36].

Pece *et al*. in a prospective open-label case series 12--month study, evaluated the efficacy of a single intravitreal injection of aflibercept followed by a PRN regimen in 32 patients (33 eyes) with subfoveal mCNV. Mean BCVA improved from 0.59 ± 0.37 logMAR at baseline to 0.38 ± 0.33 logMAR at 12 months, a change of -0.21 ± 0.23 logMAR (p < 0.0001), and from 70.5 ± 18.5 to 81.1 ± 16.4 letters, a change of 10.6 ± 11.4 (p < 0.0001). The median number of aflibercept injections was 2.0 (range 1-4). The Increase in BCVA was greater in younger patients (aged < 50 years) and those with baseline BCVA of ≤ 75 letters [37].

2.3.3. Retrospective Studies

A retrospective 18-month follow up study evaluated the efficacy of intravitreal aflibercept in 38 eyes of 38 patients with subfoveal/ juxtafoveal myopic CNV treated with 1 first injection and retreated on a PRN regimen based on OCT, FA and fundus examination findings.

Mean logMAR BCVA significantly improved from 0.69 at baseline to 0.15 at 18 months (P<0.01). Over half of the treated eyes obtained resolution with one aflibercept injection. Mean BCVA improvement was significantly greater in the eyes of the younger myopic CNV group, compared with those of ≥ 50 years (0.21 *vs* 0.35; P<0.05). The mean number of aflibercept injections was 1.8 for the <50 years myopic CNV group, and 3.6 for the ≥ 50 years myopic CNV group (P<0.001) [38] Table **3**.

2.4. Bevacizumab Studies

Bevacizumab is a monoclonal immunoglobulin antibody that bind to all isoforms of VEGF-A, reducing free VEGF-A [22].

Table 2. Ranibizumab clinical studies.

Study	Design	Treatment Groups (Eyes)	Functional Outcome: Best Corrected Visual Acuity (BCVA)
RADIANCE study (Wolf *et al*., 2014) [25] ClinicalTrials.gov Identifier: NCT01217944	12-month, phase III, randomized, double masked, multicenter, active--controlled study	Group I: ranibizumab guided by VA stabilization criteria (n = 106) Group II: ranibizumab guided by disease activity criteria (n = 116) Group III: vPDT (n = 55)	Month 3, Group I: +10.5 ± 8.2 letters; group II: +10.6 ± 7.3 letters *vs*. group III: +2.2 ± 9.5 letters; both P < 0.00001 Month 12 *vs* baseline, Group I: +13.8 ± 11.4 letters; group II: +14.4 ± 10.20 letters; (P=not significant)
POST RADIANCE study (Tan *et al* 2018) [26]	Non interventional, retrospective cohort study of East-Asian patients previously treated with ranibizumab during the RADIANCE trial	41 patients who completed the RADIANCE trial	Month 12 *vs* baseline: +14.3 ± 11.4 letters (P < 0.0001) Month 24 *vs* baseline: +10.4 ± 22.3 letters (P = 0.0143) Month 30 *vs* baseline: +11.0 ± 22.4 letters (P = 0.0134) Month 48 *vs* baseline: +16.3 ± 18.7 letters (P = 0.0034)
BRILLIANCE study (Lai *et al*., 2019) [27] ClinicalTrials.gov Identifier: NCT01922102	12-month, phase III, randomized, double masked, active-controlled study	Group I: ranibizumab guided by VA stabilization criteria (n = 182) Group II: ranibizumab guided by disease activity criteria (n = 184) Group III: vPDT (n = 91)	Month 3 (Group I/II: +9.5/ +9.8 letters *vs*. Group III: +4.5 letters; both P, 0.001). Month 12, Group I: +12.0 letters; group II: +13.1 letters; ns (continuous numerical improvement)
SMILE study (Li *et al*., 2019) [28] ClinicalTrials.gov Identifier: NCT03042871	12-month single-blind randomized clinical trial	Group I: 1 injection + pro-re-nata (PRN) (n=26) Group II: 3 injections +PRN based on VA and specific disease activity criteria (n= 24)	Month 12, Group I: +13.0±10.1 letters, Group II: + 16.4 ± 9.7 letters (P = 0.23)
REPAIR study (Tufail *et al*., 2013) [29] ClinicalTrials.gov Identifier: NCT01037348	Phase II, prospective, multicenter open-label study	After the initial injection, patients were retreated with a PRN dosing regimen based on on functional and anatomical features (n = 65)	Month 12: change in BCVA +13.8 letters from a baseline level of 59.5 letters (P < 0.001)
Iacono P *et al*. (2017) [30]	A prospective interventional, non-randomized 12-month study patients with mCNV	48 eyes treated in a PRN regimen with re-treatment based functional and anatomical features	Mean BCVA improved from 0.49 ± 0.30 logMAR to 0.39 ± 0.32 logMAR at 12-month follow-up (P = 0.043).
OLIMPIC study (Ricci *et al*, (2019) [31] ClinicalTrials.gov Identifier: NCT02034006	Prospective, 12-month, phase IIIb, open- label, interventional, multicenter study	After the initial injection, patients were retreated with a PRN dosing regimen based on functional and/or anatomical features	Month 12, + 8.4 ±12.8 letters (P < 0.0001).
Kung YK *et al*. (2014) [32]	Retrospective study	Group 1 (25 eyes) treated with single intravitreal injection; Group 2 (21 eyes) with 3 consecutive monthly injections.	Month 12, the mean BCVA was not significantly different between the two groups, Group I: from 0.58 at baseline to 0.23 logMAR at 12 months and Group 2: from 0.55 at baseline to 0.22 logMAR at 12 months; both p<0.001).
Hefner *et al*. L (2017 [33]	Retrospective study	15 eyes treated with 1 first injection and retreatment on a PRN regimen based on functional and anatomical features	Mean BCVA from 0.65 ± 0.28 logMAR at baseline to 0.35 ± 0.24 logMAR (p = 0.001) at 12 months, and to 0.39 ± 0.26 (p = 0.016) at 6 years
Onishi *et al*. Y (2019) [34]	Retrospective study	51 eyes treated with 1 first injection and retreatment on a PRN regimen based on functional and anatomical features	Mean BCVA was 0.38 logMAR units (20/49) at the baseline, 0.27 logMAR units (20/37) at 1 year, 0.31 logMAR units (20/41) at 2 years, 0.35 (20/45) logMAR units at 4 years, and 0.32 logMAR units (20/ 42) at 5 years. BCVA at 1 year *vs* baseline (P = 0.007)

Table 3. Aflibercept clinical studies.

Study	Design	Treatment Groups (Eyes)	Functional Outcome: Best Corrected Visual Acuity (BCVA)
MYRROR study (Ikuno *et al*., 2015) [35] ClinicalTrials.gov Identifier: NCT01249664	Randomized, controlled clinical trial	Patients were randomized 3:1 to Group I: intravitreal aflibercept (n = 91) or Group II: sham (n = 31)	Week 24: Group I gained 12.1 letters; Group II lost 2 letters (P < 0.0001) Week 48: Group I gained 13.5 letters; Group II gained 3.9 letters (P < 0.0001)
Korol AR *et al*., 2016 [36]	12-month cohort study	Patients received 2 initial monthly doses followed by a PRN regimen based on OCT or fundus examination disease activity criteria (31 eyes)	BCVA improved significantly at all time points (P<0.05) BCVA: 0.2 ± 0.1 at baseline and 0.35±0.16 at month 12.
Pece A *et al*., 2016 [37]	Prospective open-label case series	Patients received 1 initial monthly dose followed by a PRN regimen (33 eyes)	Mean BCVA improved from 0.59 ± 0.37 logMAR at baseline to 0.38 ± 0.33 logMAR at 12 months, a change of -0.21 ± 0.23 logMAR (p < 0.0001), and from 70.5 ± 18.5 to 81.1 ± 16.4 letters, a change of 10.6 ± 11.4 (p < 0.0001).
Bruè C *et al*., 2015 [38]	Retrospective 18-month follow up study	Patients received 1 first injection and were re-treated on a PRN regimen based on OCT, FA and fundus examination findings	BCVA significantly improved from 0.69 logMAR at baseline to 0.15 logMAR at 18 months (P<0.01)

In 2006, there was the earliest report of intraocular injection of anti-VEGF drugs for the treatment of mCNV using bevacizumab. The treatment led to a morphological improvement with complete resolution of intraretinal edema and subretinal fluid and stabilized or improved visual acuity [39].

Subsequently, several prospective and retrospective studies, mostly clinical case series, described efficacy and safety of intravitreal off-label bevacizumab [40-43].

Intravitreal bevacizumab proved to be superior to PDT in 12 months comparative trials in terms of visual outcome (P < 0.05) [40, 41].

Long-term studies evaluating different treatment regimens showed that most patients achieved significant VA improvement after intravitreal bevacizumab.

In a prospective 3-year study, 32 eyes of 30 Caucasian patients with mCNV received a loading dose of 3 monthly bevacizumab injections with retreatment with a single bevacizumab injection if required. BCVA improved significantly compared with baseline at all time points (p < 0.0001). Two years (32 eyes) and 3 years (27 eyes) after treatment BCVA was 46.6 (±12.4) letters and 45.4 (±13.0) letters, respectively, *versus* the mean baseline BCVA of 30.1 (±15.6) (p<0.0001) [44].

In a retrospective study, 103 eyes of 89 patients were treated with a single bevacizumab injection followed by PRN re-injections. In this series, after a single injection, 20.4% of eyes experienced complete resolution of CNV with an average follow-up of 44 months and an improvement of VA from 0.57 ± 0.45 at baseline to 0.38 ± 0.51 at 1-year, 0.40 ± 0.52 at 2 years, and 0.41 ± 0.41 at final visit [45].

Another retrospective study of 107 eyes with mCNV treated with one injection of bevacizumab reported that 60% required no further injections for one year with BCVA improving significantly from 0.72 ±0.43 at baseline to 0.53 ± 0.41 at 1 year after treatment (P < 0.001) [46].

Concerning the treatment regimen, no significant differences have been observed in outcomes between one loading dose and three loading doses followed by PRN re-injections [42, 47-49] Table **4**.

2.5. Studies on New Anti-VEGF Molecules

Conbercept is a full human DNA sequence that binds to VEGF-A, -B and -C, and to PlGF. Conbercept contains the fourth binding domain of VEGFR-2, which enhances the association rate of VEGF to the receptor [22].

A retrospective 24-month follow-up study assessed the efficacy of intravitreal conbercept compared to ranibizumab in 64 eyes of mCNV. At 24 months, the mean logMAR BCVA of combercept group increased from 0.95±0.54 to 0.58±0.39 (P<0.001) and the mean logMAR BCVA changed from 0.86±0.40 to 0.54±0.28 (P<0.001). The mean number of injections was 3.94±1.88 in combercept group and 4.06±1.82 in ranibizumab group (P=0.788) [50].

2.6. Comparative Studies on Intravitreal Anti-VEGF Treatments

Several prospective or retrospective study compared safety and efficacy of intravitreal anti-VEGF drugs for mCNV showing similar favourable outcomes between bevacizumab, ranibizumab and aflibercept [51-58].

A randomized clinical trial comparing ranibizumab and bevacizumab including 48 eyes reported similar VA outcomes, with a lower number of injections for ranibizumab compared to bevacizumab (2.5 *versus* 4.7 over 18 months) [54].

Another prospective multicenter randomized nonblinded trial compared the efficacy of intravitreal therapy with bevacizumab and ranibizumab for mCNV using a PRN regimen.

Table 4. Bevacizumab clinical studies.

Study	Design	Treatment Groups (Eyes)	Functional Outcome: Best Corrected Visual Acuity (BCVA)
Baba *et al*., 2010 [40]	Retrospective review of medical records	The medical charts of 40 myopic eyes of 40 patients were reviewed. Group I: photodynamic therapy (n = 16) Group II: bevacizumab (n = 27)	Month 12, Group I: BCVA change from 0.77 ± 0.25 logMAR (range 0.3-1.0) at baseline to 0.80 ± 0.28 (P > 0.05) Month 12, Group II: BCVA change from 0.75 ± 0.25 logMAR (range 0.4-1.0) at baseline to 0.49 ± 0.42 (P = 0.003)
Gharbiya M *et al*., 2012 [44]	Prospective 3-year study	Loading dose of 3 monthly bevacizumab injections followed by a PRN regimen (32 eyes)	2 years: BCVA 46.6 (±12.4) letters *vs* baseline 30.1 (±15.6) letters, (p<0.0001) 3 years: 45.4 (±13.0) letters *vs* baseline 30.1 (±15.6) letters, (p<0.0001)
Yang *et al*, 2013 [45]	Retrospective study	Single bevacizumab injection followed by PRN re-injections (103 eyes)	VA from 0.57 ± 0.45 at baseline to 0.38 ± 0.51 at 1-year, 0.40 ± 0.52 at 2 years, and 0.41 ± 0.41 at final visit
Ruiz-Moreno, 2012 [46]	Retrospective study	Single bevacizumab injection followed by PRN re-injections (107 eyes)	BCVA improving significantly from 0.72 ±0.43 at baseline to 0.53 ± 0.41 at 1 year after treatment (P < 0.001)

Best corrected visual acuity was not significantly different between the two groups (logMAR p = 0.90 and letters p = 0.78). The mean number of treatments in the first year was 2.7 with bevacizumab and 2.3 with ranibizumab (p = 0.09) [59].

Visual outcome was non significantly different at 24 months between the two groups. The BCVA was 0.21 ± 0.14 and 0.20 ± 0.14 at baseline in the ranibizumab group and aflibercept group, respectively and at 24 months 0.43 ± 0.24 (P < 0.001) in the ranibizumab group and 0.41 ± 0.2 (P < 0.001) in the aflibercept group. There were no significant differences in the mean number of injections between the two groups (2.9 ± 1.2 *vs*. 2.8 ± 1.1),(P = 0.7) [60].

A single-center study including 97 eyes with mCNV evaluated the 24-month efficacy of intravitreal ranibizumab and afliberce

A retrospective study of anti-VEGF therapy in mCNV treated either with intravitreal bevacizumab (n = 22) or ranibizumab (n = 15) injections for a follow-up of 2 years showed that the gains in BCVA (bevacizumab: 2.5 lines, ranibizumab: 3.8 lines; P = 0.25) were similar between treatment groups [61].

In two long-term retrospective studies on bevacizumab and ranibizumab treatment in mCNV by Ruiz-Moreno *et al*., both drugs were effective therapies with similar clinical effects [49, 51].

3. RECOMMENDED GUIDELINES FOR mCNV TREATMENT

Visual acuity assessment and multimodal imaging including FA, SD-OCT and OCT-A should be adopted to assess mCNV activity.

Intravitreal injection of anti-VEGF either ranibizumab or aflibercept is the first-line treatment for active mCNV with an initial intravitreal injection followed by PRN dosing regimen based on the disease activity as supported by REPAIR, RADIANCE and MIRROR randomized clinical studies [25, 29, 35].

During follow up, FA, structural OCT and OCTA should be used to drive retreatment and detect possible recurrence of mCNV.

4. Discussion

Intravitreal injection of anti-VEGF are nowadays the first-line therapy for mCNV, showing efficacy and safety in several randomized, prospective and retrospective clinical studies.

On label ranibizumab and aflibercept ~~were proven~~ proved to be efficacious in improving functional and morphologic outcomes with initial prompt intravitreal injection followed by PRN regimen in most studies. Retreatment criteria of clinical studies included loss of visual acuity, and signs of mCNV activity detected at FA and structural OCT [1, 6, 51]. The off label bevacizumab ~~demonstrated~~ showed good efficacy in mCNV treatment, nevertheless in comparative studies on label ranibizumab and aflibercept showed similar visual acuity and retinal thickness results using a lower number of injections compared to bevacizumab [51-58].

Based on clinical studies intravitreal injection of either ranibizumab or aflibercept is the first-line treatment for active mCNV with an initial intravitreal injection followed by PRN dosing regimen.

CONCLUSION

Anti-VEGF drugs are effective in the treatment of mCNV. Literature studies do not disclose significant differences between the on label ranibizumab and aflibercept in patients with mCNV, bevacizumab ~~being~~ was less effective due to the need ~~for~~ of a higher number of injections compared to the on label anti-VEGF drugs.

Based on the available literature, there is no benefit to treat mCNV with a loading dose rather than one intravitreal injection.

The recommended guidelines for mCNV treatment is one injection followed by PRN regimen based on retinal multimodal imaging.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors have no conflicts of interest, financial or otherwise.

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