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The role of anti-VEGF agents in myopic choroidal neovascularization: Current standards and future outlook

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ABSTRACT

Introduction: The global prevalence of pathologic myopia is 0.9-3.1%, and visual impairment is found in 0.1-0.5% of European and 0.2-1.4% of Asian studies. Myopic choroidal neovascularization (mCNV) affects 5.2-11.3% of pathologic myopia patients and is a leading cause of vision impairment in the working-age population. Characteristic morphological changes and visual-acuity decrease are diagnostic features. Vascular-Endothelial-Growth-Factor (VEGF) has been identified as a trigger for pathologic neovascularization in these highly myopic patients.

Areas Covered: We cover the epidemiology, pathology and diagnostic aspects of mCNV. The history of therapeutic interventions is described, followed by an overview of current standard-of-care (SOC)–blocking VEGF using bevacizumab (off-label), ranibizumab or aflibercept and improving vision up to 13.5-14.4 letters. Despite good efficacy, an unmet medical need remains. We summarize ongoing and future developments of new drugs to treat or potentially cure mCNV.

Expert Opinion: mCNV is a major global health concern. Early detection and treatment is key for a satisfying outcome. The current SOC, VEGF inhibitors, affords good therapeutic efficacy and reasonable disease stabilization with few intravitreal treatments per year. However, the long-term prognosis is still unsatisfactory, and side-effects like chorioretinal atrophy development are of concern. Therefore, efforts should be intensified to develop more effective therapies.

1. Introduction

Choroidal neovascularization in highly myopic patients [myopic choroidal neovascularization (mCNV)] is one of the leading causes of impaired vision and legal blindness, particularly in the younger population below the age of 50 years, with particular significance in Asians.\textsuperscript{1,2}

Myopia is characterized by increased axial length. Pathologic myopia even more is correlated with excessive globe elongation,\textsuperscript{3,4} and myopic degeneration precipitates the release of pro-angiogenic factors, like vascular endothelial growth factor (VEGF), which is the best studied and prevailing therapeutic target. However, several other factors contribute to the pathology and the associated vision loss.\textsuperscript{1,5} For many years, the treatment of choice for mCNV was laser photocoagulation, which is still a treatment option for exofoveal mCNV. Also, more experimental approaches such as transscleral thermotherapy or transpupillary thermotherapy were used tentatively to treat mCNV.\textsuperscript{6-12} Surgical procedures are beneficial in patients with associated vitreomacular interface pathology such as vitreomacular traction or full-thickness macular holes. Submacular and macular translocation surgeries were also performed to preserve visual function in more advanced cases.\textsuperscript{9,13-16} Alternative treatment approaches were radiotherapy and indocyanine green (ICG) mediated photothermolysis\textsuperscript{14,17,18} amongst other more experimental treatments that have been studied.\textsuperscript{18-20} The first targeted approach that successfully halted pathology and significantly and consistently improved vision in mCNV patients was the verteporfin photodynamic therapy (vPDT; Visudyne®, Novartis) that became available in 2001.\textsuperscript{[21–26]} The current standard of care (SOC) and by far the most successful and least destructive treatment is the blockage of ocular VEGF using the intravitreal drugs ranibizumab (‘Lucentis®\textsuperscript{®}, Genentech Roche/Novartis), aflibercept (‘Eylea®\textsuperscript{®}, Regeneron/Bayer), or off-label bevacizumab (‘Avastin®\textsuperscript{®}, Genentech/Roche). Despite the tremendous success of anti-VEGF agents in treating mCNV, many questions still remain to be answered. There is considerable controversy over the role of a loading dose for mCNV and over the most appropriate retreatment strategy. For the future, additional and combined efforts are needed to precisely define and standardize diagnostic criteria and the treatment regimen for this major global cause of vision loss.

In the following treatise, we will review and summarize the previous and current concepts of mCNV pathogenesis, diagnosis, and treatment and will provide an outlook on future therapeutic prospects.

2. Epidemiology

Myopia is a very common anatomic variation, affecting up to 40% of the general population. Pathologic myopia with high refractive error and axial length outside the norm is
Past treatment approaches included verteporfin photodynamic therapy. Current standards of care are intravitreal administered anti-VEGF agents, in particular ranibizumab and aflibercept, which are approved for the treatment of mCNV. A single injection followed by an as-needed approach can successfully suppress disease activity and does not seem to be inferior compared to a loading dose of monthly administered injections.

Several new approaches including slow release devices and the blockage of PDGF are currently evaluated for VEGF-mediated retinal pathologies and may in the future serve as effective therapies to treat mCNV.

This box summarizes key points contained in the article.

### Article highlights

- The prevalence of mCNV in patients affected by high myopia ranges between 5.2% and 11.3%.
- mCNV presents with acute onset of central scotoma, metamorphopsia, and decreased visual acuity. Patients should be promptly seen by a retina specialist and treatment should be initiated in a timely manner.
- Past treatment approaches included verteporfin photodynamic therapy. Current standards of care are intravitreal administered anti-VEGF agents, in particular ranibizumab and aflibercept, which are approved for the treatment of mCNV. A single injection followed by an as-needed approach can successfully suppress disease activity and does not seem to be inferior compared to a loading dose of monthly administered injections.
- Several new approaches including slow release devices and the blockage of PDGF are currently evaluated for VEGF-mediated retinal pathologies and may in the future serve as effective therapies to treat mCNV.

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3. Pathology and diagnosis

mCNV often presents as an acute disease, occurring in patients with pathologic high myopia that presents with typical symptoms including central scotoma, metamorphopsia, and decreased VA. Patients with myopia and these symptoms should be promptly examined by a retina specialist. Timely investigation and intervention is warranted because in highly active mCNV, vision loss is potentially irreversible and delayed treatment initiation may lead to inferior visual function outcome.[29,30] The pathology of mCNV is not yet completely understood, but closely linked to the pathogenesis of pathologic myopia. Mechanical stress secondary to globe distension may cause choroidal ischemia ensued by retinal pigment epithelial atrophy as well as disruption and rupture of the Bruch’s membrane. Triggered by the release of cytokines and growth factors, choroidal neovascularization (CNV) may develop.[4,28] The current understanding of mCNV evolution also explains the fact that mCNV mostly present as so-called classic type 2 lesion, with CNV being located within the subretinal space and its typical, well demarcated hyperfluorescence found in the early frames and late leakage in the late frames of the fluorescence angiography (Figure 1).[31–34] Accordingly, subretinal hyperreflective lesions accompanied by subretinal fluid and intraretinal edema are encountered on Spectral Domain Optical Coherence Tomography (SD-OCT) (Figure 1).[32,34,35] Even in Asians, polypoidal choroidal vasculopathy lesions in the retina are rarely found in mCNV.[36]

A comprehensive ocular history needs to be taken, and careful eye examination including funduscopy must be performed. Retinal imaging using fluorescein angiography (FA), ICG, and SD-OCT will confirm the diagnosis of mCNV and aid differentiation from other causes of vision loss in highly myopic patients such as lacquer cracks, that is ruptures in the Bruch’s membrane due to shear stress and subretinal hemorrhage.[37–40] Further possible reasons for visual function decline linked to pathologic myopia such as myopic retinoschisis, macular hole, epiretinal membrane, or chorioretal atrophy should be searched for. Imaging modalities corresponding to the baseline evaluation should be used to monitor and follow the treatment response of the patients.[34,41] Data on the sensitivity of SD-OCT and FA to detect mCNV are heterogeneous.[32,42] It is a fact that mCNV associated findings on FA and SD-OCT correlate poorly,[32,41] and therefore, both imaging modalities should be utilized at least on initial presentation in order to confirm mCNV. In comparison to FA, ICG may be the superior modality to differentiate mCNV from subretinal hemorrhage and lacquer cracks.[34,40,43]

Continuous treatment monitoring should be ensured using SD-OCT. The presence of intra- or subretinal fluid, but also hyper-reflective lesions with indistinct borders and irregularities in the photoreceptor structures such as

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Figure 1A. Color fundus images of a patient with mCNV at initial presentation. The right eye reveals a normal posterior pole of a patient with myopia. The left eye shows a classic, type 2 CNV membrane (blue arrow) with some subretinal hemorrhage (white arrows).
the external limiting membrane, the interdigitation zone, or the ellipsoid zone are indicators for disease activity.\cite{35,41,44} However, exudative hyporeflective intraretinal cystic spaces due to active mCNV must be distinguished from degenerative myopic macular schisis, which presents with intraretinal splitting of the inner and outer retinal layers, resulting equally in intraretinal cystoid spaces, but usually has preserved outer retina architecture.\cite{45} Additional imaging techniques can be useful and informative, including fundus autofluorescence (FAF) to detect areas of atrophy and enhanced deep imaging or swept source Optical Coherence Tomography (OCT) to evaluate choroidal thickness. Novel techniques such as OCT angiography or adaptive optics may be important supplementary image modalities in the future for the evaluation of mCNV and its visual outcome.

Provided an accurate diagnosis, the adequate treatment can result in very significant long-term benefit for affected patients and early, aggressive treatment reduces the risk of long-term structural damage and vision loss.

4. Laser and vPDT (visudyne®)

Before intravitreal drug therapies were available, laser photocoagulation, thermotherapy, and surgical procedures have been used to treat mCNV.\cite{6–13,15} These treatments were applied in an attempt to stop disease progression; however, their use and perceived benefit for patients was limited. Laser photocoagulation for subfoveal and juxtafoveal mCNV had a poor prognosis and was associated with a high rate of recurrence.\cite{11,46}

Before the current SOC for mCNV – intravitreal injections of anti-VEGF – became available, vPDT was the treatment of choice and remains a safe treatment alternative for patients with off-center, juxtafoveal, and extrafoveal mCNV until today.\cite{47–49} For vPDT, verteporfin is injected intravenously to

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig1B.png}
\caption{Left: Regular fluorescein angiography (FA) of the right eye of the same patient. Middle: The FA of the left eye reveals the well circumscribed neovascular membrane (red arrow) characteristic for mCNV. Right: The late frame of the FA shows late leakage of the mCNV lesion (red arrow).}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig1C.png}
\caption{SD-OCT of both eyes at initial presentation. Top: A regular central SD-OCT scan with preserved foveal contour and intact retinal layers. Bottom: The central scan of the left eye reveals subretinal fluid and irregularity of the outer retina (yellow arrow). The choroidal neovascular lesion is also nicely visible on the corresponding infrared image (red arrow).}
\end{figure}
reach the ocular blood vessels via the systemic circulation. Verteporfin is then locally activated in the ocular vasculature by laser irradiation at 689 nm. This light-activation induces the release of highly reactive, short-lived oxygen radicals, which cause damage to the local choroidal neovascular endothelial cells and thereby produce capillary vessel occlusion and subsequent atrophy of the CNV complex in the choroid. vPDT therapy was shown to be superior to placebo in a pivotal, well-controlled, randomized 2-year clinical trial. The vPDT group was more likely to show stable best-corrected visual acuity (BCVA) compared to the control group; however, the 24 months data failed to show a significant benefit on BCVA. In most patients, retreatment was necessary, especially in the initial follow-up period of 6 months.

However, in clinical practice, mCNV barely requires more than two vPDT treatments to remain inactive in FA. Baseline VA and age seem to affect treatment outcome in vPDT: Patients with higher baseline VA and younger age seem to have a better treatment outcome. A retrospective long-term cohort study analyzed vPDT treatment outcomes in juxta- and subfoveal mCNV and found satisfactory results. BCVA improved from 0.59 ± 0.42 to 0.33 ± 0.27 logMAR in patients with juxtafoveal mCNV, while eyes with subfoveal mCNV suffered a continuous BCVA decline from 0.68 ± 0.26 to 0.80 ± 0.47 logMAR during the 10-year follow-up. The prevalence of chorioretinal atrophy was 84%. This study once more confirmed the limited potential of vPDT for subfoveal mCNV, but established vPDT as a valuable treatment alternative second to anti-VEGF injections for juxta- and extrafoveal mCNV.

However, shortly after the discovery of anti-VEGF agents as potent tools for treatment of ocular CNV, the inferiority of vPDT compared to intravitreal treatment was shown. Using off-label bevacizumab, a recombinant humanized monoclonal anti-VEGF antibody, Ikuno et al. demonstrated a sustained increase of BCVA for bevacizumab while in vPDT patients’ VA declined toward the end of the 2-year study after initial stabilization.

A recent meta-analysis of clinical studies comparing vPDT with intravitreal anti-VEGF for mCNV confirmed these results. The authors analyzed 5 studies with a total of 349 eyes and found significantly higher gain of VA with anti-VEGF than with vPDT.

Interestingly, another study on the long-term outcomes of vPDT versus anti-VEGF (ranibizumab) treatment that included 85 eyes with at least 2 years of follow-up concluded that anti-VEGF was significantly better at improving VA despite similar CNV regression rates (93% vs. 88%). These results suggest that CNV regression is not the only treatment effect, and additional factors influence VA outcomes in mCNV patients. Both treatments were associated with an increase in chorioretinal atrophy size but atrophy growth was significantly greater in the vPDT group. Other studies also found that atrophy may increase independent of the treatment modality.

5. Anti-VEGF agents

The discovery of VEGF in the mid-1990s as a key factor for angiogenesis in pathologic neovascularization was a breakthrough, changing the understanding of pathology and the therapeutic approach for many retinal pathologies, including mCNV. Early clinical studies with a PEGylated anti-VEGF aptamer (EYE 001 from Eyetech Pharmaceuticals) showed promising results in patients with exudative age-related macular degeneration (AMD). In 2004, this aptamer became the first FDA approved anti-VEGF drug for ophthalmic use, marketed as pegaptanib sodium (Macugen®; Eyetech and Pfizer) for the treatment of AMD. Other anti-VEGF molecules/antibodies that were not based on aptamer technology became available soon and offered better overall safety and efficacy profiles. Current SOC treatments are no longer based on this technology. The promising results of blocking VEGF in AMD together with the knowledge that mCNV is associated with increased intravitreal VEGF and decreased pigment epithelium derived factor levels subsequently led to studies which successfully tested anti-VEGF in mCNV.

5.1. Pegaptanib

Pegaptanib was not approved for the treatment of mCNV. Based on the fact that more efficient drugs for the treatment of CNV were swiftly available, only few small clinical trials using pegaptanib for mCNV were performed. Kitagawa et al. found no significant change in BCVA (baseline: 0.49 ± 0.38 and post-treatment: 0.47 ± 0.35 logMAR) and retinal sensitivity after a mean of 3.1 intravitreal pegaptanib injections after 1 year. The lesion diameter however decreased significantly from 1217 to 1041 µm. In another nonrandomized trial by Rinaldi et al., the administration of three consecutive 6-weekly intravitreal pegaptanib injections leads to a significant BCVA (25.5 ± 8.09 letters to 45.5 ± 8.16 letters) and retinal sensitivity increase after 48 weeks with no need of further injections.

5.2. Bevacizumab

Bevacizumab, an anti-VEGF antibody developed and approved for several oncology indications was used early for ocular indications and is now frequently applied by ophthalmologists as a cheap off-label alternative for neovascular retinal diseases. Controlled masked multicenter trials for the usage in mCNV are lacking, but several reports following patients for up to 5 years showed a clear benefit of intravitreal bevacizumab over vPDT and placebo in mCNV. A retrospective analysis of 21 eyes treated with bevacizumab in a pro re nata (PRN) treatment regimen demonstrated an improvement of ≥1 line in over 71% of the included patients after 4 years. Combination therapies were also tested; a consecutive retrospective case series over 2 years evaluated the effect of bevacizumab alone or in combination with PDT. While the monotherapy group improved from 0.7 to 0.5 logMAR after 2 years, the BCVA changed only from 0.55 to 0.59 logMAR in the combination group. CRT significantly decreased in both groups (monotherapy: mean decrease: 168 µm vs. combination therapy: 76 µm).

As of today, two VEGF inhibitors were tested in controlled, masked clinical trials for mCNV and are now approved with highest evidence for this indication in many countries worldwide. The first approved drug was ranibizumab, based on...
results from the pivotal RADIANCE trial.[66] The second approved treatment was aflibercept, based on the MYRROR study.[67] A representative example of a patient with mCNV treated with intravitreal anti-VEGF can be found in Figure 2.

5.3. Ranibizumab

Ranibizumab is a Fab fragment of a humanized monoclonal antibody against VEGF-A. Ranibizumab was the first approved anti-VEGF monoclonal antibody for ocular indications. Approval was granted by the FDA for exudative AMD first in 2006. The evidence of benefit in mCNV was drawn from a phase 2 study (REPAIR; NCT01037348) and a phase 3 study (RADIANCE NCT01217944).[66,68] These studies demonstrated the clinical efficacy and safety as well as superiority of ranibizumab in comparison to vPDT. In 2013, ranibizumab became approved for the treatment of mCNV in more than 80 countries including Europe and Japan. However, so far ranibizumab is not approved in the United States.[66,67]

The pivotal RADIANCE trial included 277 patients with visual impairment due to mCNV allocated to 3 different treatment groups. Group 1 (n = 106) received two monthly intravitreal ranibizumab injections followed by as-needed treatment (PRN) guided by VA. Group 2 (n = 116) received ranibizumab as-needed from the start, guided by disease activity criteria. Group 3 (n = 55) was treated with vPDT at inclusion and from month 3 onward received ranibizumab and/or vPDT at investigators’ discretion (www.clinicaltrials.gov, NCT01217944). Patients with VA-guided retreatment (group 1) gained 13.8 letters and needed a median of 4.0 injections over 12 months. Patients with PRN treatment guided by disease activity criteria gained 14.4 letters with a median of only 2.0 injections.[66] Subsequent long-term studies have confirmed that in many patients only a small number of anti-VEGF injections are necessary to halt the disease and maintain BCVA in the long term. A mean number of 4.9 anti-VEGF injections were reported during a 4-year observational period.[69]

Further supporting evidence for the efficacy of ranibizumab has been gained from numerous smaller studies and case series on the use of ranibizumab in mCNV patients.[53,70–73]
5.4. Aflibercept

Aflibercept is the second intravitreal anti-VEGF drug approved for mCNV. Aflibercept is a genetically engineered fusion protein consisting of the naturally occurring human VEGF receptor 1 and 2 binding sites and the Fc portion of the human IgG1 immunoglobulin linking the binding sites. Aflibercept has a higher binding affinity for VEGF than ranibizumab and presumably a longer intravitreal half-life. [74–76] Aflibercept 2 mg is approved for the common retinal conditions AMD, diabetic macula edema, and retinal vein occlusion. Approval for mCNV is based on the MYRROR study, a phase 3 clinical trial that included 122 patients (NCT01249664). [67] Ninety-one patients were treated with aflibercept and 31 subjects with sham injections. After an initial intravitreal injection at baseline, as-needed treatment was provided for up to week 44. At week 24, patients on aflibercept treatment had gained on average 12.1 ETDRS letters, whereas sham patients had lost 2 letters. After switching sham patients to intravitreal aflibercept treatment at week 24, they gained overall 3.9 letters by week 48 while aflibercept patients had gained a total of 13.5 letters at the end of the study (week 48). So far aflibercept is approved in Europe and Japan (approval in Japan: September 2014, in Europe October 2015), but not in the United States.

6. Comparison of treatment regimens

To determine the optimal treatment regimen in mCNV, Wakabayashi et al. investigated the visual outcome and the number of injections needed after a single versus three monthly bevacizumab-loading injections. A similar improvement of BCVA was found in both groups with similar rates of recurrence and persistence of mCNV in 12 months. However, the number of injections needed was significantly lower after the single-loading dose. [77] Another study evaluated two different dosing regimens in mCNV using ranibizumab. In this study, the group with three loading doses in contrast to the group with a single-loading dose injection needed less retreatment over a period of 1 year. The visual outcome, however, was similar in both groups. [71] The RADIANCE trial yielded similar results for both anti-VEGF treatment groups. Thus, the patient group with a single-loading injection had a similar BCVA improvement as the group with two initial loading injections of ranibizumab. [66] Similar conclusions were drawn from another recently published study, which guided treatment regimen based on the initial response to the first ranibizumab injection. [78] The first group (=the PRN group) showed no CNV activity after the initial ranibizumab injection and received additional treatment according to PRN treatment regimen. The second group had active CNV after the initial treatment and received a loading dose of three consecutive monthly ranibizumab injections followed by a PRN treatment regimen (=LOAD + PRN group). After 18 months, 58% eyes of the PRN group but only 25% of the LOAD + PRN group displayed a >3 line gain. The baseline characteristic of both groups differed significantly in age, duration of symptoms and CNV area. [78] All these findings suggest that a single injection followed by an as-needed approach can be successfully employed leading to similar visual function outcomes compared to two or three monthly loading doses. Most importantly, the study reiterates that an early diagnosis with a small CNV size is associated with a favorable functional outcome. [78]

7. Prognostic factors during anti-VEGF therapy

As described above, the current treatment of mCNV is essentially based on intravitreal anti-VEGF injections. However, a best-practice pattern still needs to be established. Frequencies of injections and monitoring have been studied in several trials for different anti-VEGF agents. To identify the optimal treatment for the individual patient, a personalized disease activity measurement and progression rate estimation should be the basis of the treatment plans.

In this regard, several studies have been undertaken to assess disease risk and recurrence rates in mCNV patients. An elegant and elaborated study by Yang et al. with 103 eyes revealed an association of the recurrence rate with age, myopic refraction, thinner choroid, larger CNV area, and subfoveal hemorrhage in univariate analysis. In multivariate analysis, the only significant predictive factor for recurrence was baseline CNV size. [79] Recurrence rate, baseline BCVA, choroidal thickness, and CNV size were significantly associated with final BCVA. Baseline choroidal thickness, CNV size, age, and presence of lacquer cracks were significantly associated with the number of injections. [79] Another similar study found CNV size, duration of symptoms, and baseline BCVA to be the most important factors predicting BCVA improvement. [80] The progression of macular atrophy was predictive for the VA outcome under intravitreal ranibizumab. [38] Interestingly, eyes with higher myopic error were less likely to gain vision after ranibizumab or bevacizumab treatment. [72] In a meta-analysis on mCNV treated with anti-VEGF, the authors confirmed that limited chorioretinal atrophy, smaller pretreatment CNV size, and younger age were associated with a good treatment outcome using bevacizumab. [81] In addition, VEGF gene polymorphism seems to influence the VA prognosis with anti-VEGF therapy. The single nucleotide polymorphism in the VEGF gene, rs2010963, seems to be significantly associated with greater VA improvement. [82] Furthermore, also the autofluorescence pattern is a prognostic indicator for the treatment outcome in mCNV: A preserved hyperautofluorescent pattern during intravitreal treatment with ranibizumab in contrast to a patchy pattern was an indicator for a significant visual function improvement. [83]

8. Possible risks and long-term issues of anti-VEGF therapy in mCNV

Intravitreal drug application carries the usual risks of traumatic cataract, retinal detachment, and endophthalmitis, which can be devastating for visual function and globe integrity. Intravitreal anti-VEGF treatment has also been associated with sustained
elevation of intraocular pressure,[84] and myopic discs are considered particularly vulnerable to pressure rises. Current studies are also discussing a potential negative impact of anti-VEGF agents on the formation and progression of macular atrophy in the treatment of exudative AMD.[85] VEGF is important for the integrity of the retina pigment epithelium (RPE) and the choriocapillaries.[86,87] Inhibition of VEGF may therefore promote atrophy progression. Although the chorioretinal atrophy in mCNV differs from the RPE atrophy observed in neovascular AMD, a potential effect on chorioretinal atrophy progression in mCNV is conceivable. A recent long-term study on mCNV patients treated with bevacizumab found significant chorioretinal atrophy progression after 5 years of follow-up.[63] However, progression of chorioretinal atrophy is also found after vPDT, and the extent seems even worse than after anti-VEGF treatment.[38,53] It remains unknown whether anti-VEGF agents exacerbate chorioretinal atrophy formation while suppressing exudative disease activity. Though bad long-term functional outcome of eyes with mCNV is associated with progression of chorioretinal atrophy,[38] Further studies investigating the effect of anti-VEGF agents on eyes with mCNV are therefore necessary. Moreover, a recent retrospective study discussed anti-VEGF agents as a potential risk factor for the progression of macular retinoschisis in myopic eyes with CNV and epiretinal membranes.[88] However, a recent post-hoc analysis of the large, controlled RADIANCE trial by our group did not confirm these claims. None of the RADIANCE patients treated with ranibizumab showed progression of macular schisis (manuscript in preparation).

9. **Unmet medical need and perspective**

While the current anti-VEGF antibodies ranibizumab, the off-label bevacizumab and the VEGF – inhibiting VEGR-Receptor fusion protein aflibercept – can be considered the SOC for mCNV, the clinical and anatomical benefit can be further improved, the therapy-responder rate needs to be optimized as well as the duration of the therapeutic response, the route of application and the overall safety. Further, a very significant unmet medical need exists in poorly funded health care systems due to financial, educational, and emotional barriers to consult adequately qualified health care providers.

Despite considerable prevalence of mCNV, primarily in Asia, limited research and development activity is currently undertaken in this particular field. A search for mCNV and pathologic myopia in the most relevant clinical trial registry (ClinicalTrials.gov) amongst 200 000 listed clinical studies revealed only about 30 active studies with pharmaceutical compounds, almost exclusively already clinically used anti-VEGF agents as aflibercept, ranibizumab, and bevacizumab plus one study with a new anti-VEGF fusion protein, conbercept.

Several approaches have been developed and are currently evaluated in clinical studies to improve the efficacy and the duration of existing therapies in order to improve clinical benefit by addressing existing and validated therapeutic targets as VEGF. Combination therapies with vPDT have been tested; however, the results were not superior to anti-VEGF monotherapy.[89] Slow release devices or formulations to reduce the need for frequent re-injections of anti-VEGF drugs are in late-stage clinical development. The overall goal is to establish a reservoir either outside or inside the eye that assures continuous release of existing inhibitors and therefore blockage of VEGF for many months without the need for frequent re-injections. Also, addition of new therapeutic targets to existing anti-VEGF therapy – like platelet derived growth factor (PDGF) is an interesting strategy and has shown some benefit in neovascular AMD – using a PDGF blocking agent that is injected in addition to ranibizumab (‘Fovista’, Ophthotech).[90]

In the past years, several new molecular entities, many of them anti-cancer treatments inhibiting neovascularization based on different modes of action, have been tested in early stage clinical trials. Combretastatin A4 Phosphate, a microtubule-stabilizing agent was in a phase 2 trial for mCNV but obviously results were not convincing.[91,92] So far, none of these experimental drugs made it to late-stage trials or close to approval for the treatment of mCNV.

Even though the absence of specific developments for new treatments targeting mCNV seems frustrating for affected patients, the search for new and improved therapies for ocular/choroidal CNV in general is very active and several new approaches including new therapeutic targets, and new combination therapies are currently studied. Several improved molecules that block VEGF or target the VEGF receptors signaling pathway are in development. Brolucizumab (ESBA 1008, Alcon) is a small, single-chain antibody fragment that blocks VEGF and is in late-stage development for AMD. Small interfering RNA have been in clinical development for many years. They block transcription, production, and release of VEGF. In addition, systemic oral and/or topical therapies are developed that promise easier administration (i.e. no need for intravitreal injections) and thereby reduction of treatment burden for patients. Some are in late-stage clinical trials. All these molecules are developed for neovascular, in part VEGF-mediated retinal pathologies, but mostly specifically target AMD (as this currently is the biggest market). If successful for AMD, all these newcomers are promising candidates to treat pathological changes in mCNV.

Another interesting approach from Ocata Therapeutics (former ACT) to treat or even cure the pathologic changes in mCNV is based on stem cells, differentiated into retinal pigmented epithelium (RPE) cells. An early phase 1/2 study assessing safety and tolerability will start soon using embryonic stem cell derived MA09-hRPE cells transplanted sub-retinally in patients with geographic atrophy secondary to myopic macular degeneration.[93]

The most promising approaches – unfortunately in the distant future – are possibly based on the identification of the genetic causes for mCNV, and even more so, on the genetic basis for high myopia as such.

Genetic remedy of abnormalities that lead to myopia obviously would eliminate myopia as one of the most prevalent health problems altogether and thereby eradicate complications associated with high myopia – like mCNV. Currently, more than 70 genes or gene loci have been associated with myopia, several of which associated with collagen development but also homeobox genes like PAX-6, which is involved in oculogenesis.[94] Overall, it has been postulated that up to 80% of the pathologic changes in highly myopic patients are caused by genetic alterations.[95] Therefore, the prospect of gene therapy to correct the abnormal gene expression
pattern, and therefore the development of myopia, would be the ultimate goal of the intense research in this field.

10. Conclusion
mCNV is a significant global health care problem and a threat for the working-age population as it is one of the leading causes of vision impairment and legal blindness. Fortunately, the recent development of targeted therapies that block VEGF, one of the underlying factors that lead to CNV formation in pathologic myopia, has led to a breakthrough in the clinical management. Whereas in the past treatment possibilities and the overall prognosis were limited, with effective therapy nowadays the pathologic processes can be stopped or even reversed, and a gain in vision and long-term stabilization can be achieved.

11. Expert opinion
mCNV is one of the leading causes of vision loss and legal blindness, in particular in a younger population and with significantly higher prevalence in the Asians. The treating ophthalmologist needs to be aware of the complications in highly myopic patients. When evidence for mCNV is found, appropriate evaluation using multimodal imaging is advised, and treatment should be initiated in a timely manner because treatment delay may result in irretrievable vision loss. The current SOC is intravitreal injection of anti-VEGF agents, with ranibizumab and aflibercept being approved in many countries. Bevacizumab is also frequently used because it may have similar effectiveness in mCNV and is relatively cheap, but its use is off-label. These agents have a good safety profile and often produce a fast recovery of visual function. Also in the long term, anti-VEGF agents achieve excellent control of disease activity with few side effects and massively improve the prognosis for mCNV patients. Treatment patterns for the various drugs differ with respect to timing and the number of injections, and are a field of intensive clinical research. One open question remains to be answered for the current SOC: Which is the best drug for a given patient and/or are there clinically significant differences in efficacy? A similar question has been addressed in very large multicenter trials for other more common ocular pathologies, in particular CNV secondary to AMD. For neovascular exudative AMD, the multicenter CATT study included more than 1200 patients and revealed only minor differences between ranibizumab and aflibercept use. Similar but smaller studies found comparable efficacy for both drugs in mCNV.[96] In the registration trial including 2457 patients, aflibercept was compared to ranibizumab for neovascular AMD.[97] This represents the largest clinical trial for AMD to date. Both drugs were similarly effective in all tested treatment regimens.[97] For mCNV, the evidence often comes from smaller single-center comparative studies. One such retrospective study compared the efficacy of bevacizumab versus ranibizumab for mCNV and found comparable BCVA improvement (bevacizumab: 0.67 ± 0.28 at baseline to 0.46 ± 0.43 logMAR after 12 months versus ranibizumab: 0.63 ± 0.30 at baseline to 0.39 ± 0.42 after 12 months), and central retinal thickness decrease in both groups during follow-up.[73] Another comparative study between bevacizumab and ranibizumab revealed similar efficacy in improving VA, but this was achieved with significantly fewer injections in the ranibizumab versus the bevacizumab group (2.5 vs. 4.7 injections in 18 months).[98] Another study showed a (non-significant) trend to better VA gain (bevacizumab: 2.8 line gain vs. ranibizumab: 5.1 line gain, p = 0.073) with ranibizumab during a follow-up of 2 years with the same number of injections.[72] Studies comparing aflibercept with other anti-VEGF agents for mCNV have not been published yet. The potential superiority of any of the available anti-VEGF drugs over the others remains to be studied in a larger, multicenter setting. It would be interesting and informative also to study whether significant differences are evident in larger cohorts, and whether aflibercept may be a better choice for specific groups of patients, for example for mCNV patients with lower baseline BCVA. Compared to other retinal conditions treated with anti-VEGF, significantly fewer injections are needed for mCNV, likely related to a lower VEGF burden in this disease.[99,100] Prognostic and predictive factors for treatment need and outcome are under investigations, with several studies already providing good guidance for the treating physician. A number of promising, longer lasting, and more effective therapies for CNV are investigated in clinical trials that may eventually result in additional treatment options in the future.

In conclusion, treatment for mCNV has made tremendous progress during the last decade and now often results in disease stabilization and significantly better visual outcomes for affected patients if they are diagnosed and treated in a timely manner.

Declaration of interest
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References
Papers of special note have been highlighted as either of interest (i) or of considerable interest (ii) to readers
2. This study gives a great overview over the epidemiology of mCNV.
This paper presents the so far longest follow on patients with myopic CNV.


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This paper reports the data of the approval trial of ranibizumab in myopic CNV.


