# Anti–vascular Endothelial Growth Factor Therapy for Myopic Choroidal Neovascularisation

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## Abstract

Pathological myopia represents the most common cause of choroidal neovascularisation in young patients. Its natural course has a devastating prognosis. Several treatments have been assessed, but photodynamic therapy is currently the only approved treatment for subfoveal choroidal neovascularisation related to pathological myopia. Anti-vascular endothelial growth factor therapy has demonstrated promising results in any form and localisation of choroidal neovascularisation, although there is an absence of data obtained from randomised clinical trials. The aim of this article is to compare different treatment options, combinations and retreatment criteria for the management of choroidal neovascularisation in eyes with high myopia.

## Keywords

Choroidal neovascularisation, pathological myopia, photodynamic therapy, anti-vascular endothelial growth factor, ranibizumab, bevacizumab, pegaptanib

**Disclosure**: The authors have no conflicts of interest to declare.

**Received**: 18 June 2013 **Accepted**: 17 July 2013 **Citation**: *European Ophthalmic Review,* 2013;7(2):84–6 *DOI: 10.17925/EOR.2013.07.02.84*

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High myopia affects approximately 2 % of the general population, and represents an important cause of visual impairment in many developed countries. Choroidal neovascularisation (CNV) is one of the most vision-threatening complications of myopia.[1–3] Nearly 10 % of eyes with pathological myopia (PM) develop CNV,[4] and represents the most common cause of CNV in young patients, accounting for almost 60 % of CNV in patients under the age of 50.[5] It is also known that more than 30 % of myopic patients with pre-existing CNV will develop CNV in the fellow eye within 8 years. The natural course of this disease has a devastating prognosis, accounting for low visual acuity (VA) (20/200) in 44–60 % of the patients after 24 months.[6]

## Current Targets and Treatments

Current treatment of CNV in PM is still not well defined. Laser photocoagulation is the standard treatment for extrafoveal CNV,[7] while photodynamic therapy (PDT) with verteporfin (Visudyne®, Novartis AG, Basel, Switzerland) is the only approved treatment by the European Agency for the Evaluation of Medicinal Products (EMEA) and the US Food and Drug Administration (FDA) for subfoveal CNV related to PM. Several other treatments have been assessed, such as macular translocation,[8–9] surgical removal of CNV,[10] radiotherapy[11] and indocyanine green mediated photothrombosis.[12,13] Recently, anti-vascular endothelial growth factor (anti-VEGF) therapy has become the most widespread treatment throughout he scientific community.

## Photodynamic Therapy

The only evidence derived from randomised controlled trials is provided by the Verteporfin in Photodynamic Therapy (VIP) Study.[14,15] This study showed a significant benefit in eyes treated with verteporfin compared with placebo at 12-month follow-up (86 % of the verteporfin-treated patients lost fewer than 15 letters of best-corrected VA [BCVA], in comparison with 67 % of the placebo-treated patients). However, the effect of PDT was not sustained by the end of the second year. As PDT monotherapy showed limited VA improvement, subretinal fibrosis and chorioretinal atrophy were observed, and the need to find an association with other therapies increased. An attempt to improve the efficacy of PDT by enhancing the fluence[16] or combining PDT with intravitreal triamcinolone acetonide injection[17,18] showed inconsistent results. However, Rishi et al.[19] described good results in combining PDT with anti-VEGF injection in a retrospective study of 26 patients. Coutinho et al.[20] also had interesting results, describing a VA gain of ≥3 lines in 32.6 % of the eyes treated with PDT in a retrospective study of 43 eyes at 5-year follow-up.

## Anti-vascular Endothelial Growth Factor Therapy

The factors that stimulate pathological neovascularisation are not completely understood, but VEGF has been found to be one of the main elements in angiogenesis, and several reports have provided evidence that VEGF-A plays an important role in promoting CNV in PM.[21–26] Moreover, studies carried out by Tong et al. showed increased VEGF concentrations in aqueous humour of patients with CNV secondary to PM when compared to controls.[27]

So far, ranibizumab (Lucentis®, Novartis, Basel, Switzerland) and bevacizumab (Avastin®, Genentech, South San Francisco, CA, US) are the most diffuse anti-VEGF drugs, giving a pan-VEGF blocking.[28–30] Ranibizumab is a specific, affinity-mature fragment of a recombinant, humanised immunoglobulin G1 (IgG1) monoclonal antibody that neutralises all active forms of VEGF-A, which was approved by the FDA for the treatment of exudative age-related macular degeneration (AMD) in June 2006. Bevacizumab is a full-length humanised antibody

**Table 1: Comparison of Published Studies Using Anti-vascular Endothelial Growth Factor Therapy for Myopic Choroidal Neovascularisation**

| Author | Drug | Design | Number | Visual Acuity Outcomes | Visual Acuity Improvement | Number of Injections | Follow-up |
|---|---|---|---|---|---|---|---|
| Konstantinidis[32] | Ranibizumab | Prospective | 14 | ETDRS letters | 0'48 decimal equivalent | 2.3 | 8.4 months |
| Monés[33] | Ranibizumab | Prospective | 23 | ETDRS letters | 9,53 letters | 1.5 | 12 months |
| Vadalà[6] | Ranibizumab | Prospective | 40 | ETDRS letters | 2,9 lines | 2.8 | 13.3 months |
| Silva[36] | Ranibizumab | Prospective | 34 | ETDRS letters | 8 letters | 3.6 | 12 months |
| Calvo-González[37] | Ranibizumab | Prospective | 67 | ETDRS letters | 12 letters | 4.2 | 15.9 months |
| Sakaguchi[23] | Bevacizumab | Prospective | 8 | Snellen equivalent | 0'25 decimal equivalent | 1.3 | 4.4 months |
| Yamamoto[22] | Bevacizumab | Retrospective | 11 | Snellen equivalent | 3,5 lines | 1.2 | 153 days |
| Arias[38] | Bevacizumab | Prospective | 17 | ETDRS letters | 13,7 letters (loading dose)<br>4,6 letters (*pro re nata*) | 1.1 | 6 months |
| Hernández-Rojas[26] | Bevacizumab | Prospective | 14 | Snellen equivalent | logMAR –0,95 (initial)<br>logMAR –0,56 (final) | 1.2 | 3 months |
| Ikuno[39] | Bevacizumab | Retrospective | 63 | Snellen equivalent | logMAR 0,23 | 2.4 | 12 months |
| Gharbiya[41] | Bevacizumab | Prospective | 20 | ETDRS letters | 18,2 letters | 4 | 12 months |
| Ruiz-Moreno[43] | Bevacizumab | Retrospective | 107 | ETDRS letters | 7,7 letters | 1.8 | 12 months |
| Iacono[45] | Bevacizumab/ ranibizumab | Prospective Randomised | 55 | ETDRS letters | 1,7 lines (ranibizumab)<br>1.8 lines (bevacizumab) | 2.5 (ranibizumab)<br>4.7 (bevacizumab) | 18 months |

*ETDRS = Early Treatment Diabetic Retinopathy Study.*

that inhibits all isoforms of VEGF-A and is approved for treatment of colorectal cancer, and its use as intravitreal anti-VEGF drug is off-label. On the other hand, pegaptanib (Macugen®, Eyetech Pharmaceuticals /Pfizer) is an RNA aptamer specifically directed against the VEGF-165 isoform, approved by the FDA in December 2004 for the treatment of CNV secondary to AMD. There are very few reports regarding the use of pegaptanib for CNV secondary to PM.[31] *Table 1* shows the main results of the published studies using anti-VEGF therapy for myopic CNV.

## Ranibizumab

Several studies have reported promising results with the use of ranibizumab. Konstantinidis et al.[32] treated 14 eyes for CNV secondary to PM with intravitreal ranibizumab, reporting a visual mean improvement of 3.86 lines with a mean of 2.36 injections and a mean time of follow-up of 8.4 months. Monés and co-workers[33] conducted a prospective study of 23 eyes treated with intravitreal ranibizumab as needed, with an average of 1.52 injections and a follow-up duration of 12 months. Mean VA gain was 9.53 letters and in patients younger than 50 years old the improvement was higher than in older patients. They suggest that in CNV, treat 'on demand' from the first injection may achieve good clinical results, minimising the number of needed injections and their potential related systemic and local complications. It is also emphasised that paninhibition of VEGF might impact on the survival of retinal neurons,[34] and points out the need to only administer the smallest number of injections as possible.

Vadalà et al. prospectively enrolled 39 patients with CNV related to PM, treated 'on demand'. Sixty per cent of the patients gained three or more lines with a mean follow-up of 13.3 months. The mean number of injections was 2.8. They did not notice any difference in visual outcome between eyes previously treated with PDT and naive eyes. Patients suffering myopic CNV are often younger than those affected from AMD-CNV, and therapies can be more effective because of the healthy retinal pigment epithelium (RPE) in those patients. In the same way, Lai et al.[35] observed a gain in vision in 75 % of patients, and only one patient needed retreatment during the 12 months follow-up. More recently, Silva et al.[36] prospectively treated 34 eyes with intravitreal ranibizumab. Twenty-four per cent of the eyes improved three or more lines, with a mean treatment of 3.6 injections in a 12-month follow-up period. Calvo-Gonzalez et al.[37] reported 67 patients treated with three intravitreal ranibizumab injections given monthly. In a follow-up period of 16 months, a total of 53 % of eyes received only three injections and mean BCVA improved by 12 letters. They stated the importance of baseline BCVA and myopic CNV location as predictive factors for visual outcome.

## Bevacizumab

There are several papers regarding the use of bevacizumab for CNV secondary to PM. Sakaguchi[22] and Yamamoto[23] were the first reporting case series with 1.25 mg intravitreal bevacizumab showing VA improvement. Arias and colleagues[38] reported a prospective study of 17 patients, at 6-month follow-up, the mean Early Treatment Diabetic Retinopathy Study (ETDRS) VA improved by 8.4 letters and the mean number of injections was 1.1 of 1.25 mg bevacizumab, suggesting that frequent injections may not be necessary in these cases, at least while no longer follow-up data are available. Similarly, Hernández-Rojas et al. published good visual results in a prospective study of 14 eyes treated with 2.5 mg bevacizumab at the 3-month follow-up. Ikuno et al.[39] performed a retrospective study on 63 eyes treated 'on demand'. Overall, 40 % of patients improved vision, while 56 % remained stable. The mean number of injections was 2.4 in a 1-year period. Gharbiya et al.[40] in a 1-year follow-up prospective study on 20 eyes treated with a mean number of four 1.25 mg intravitreal bevacizumab reported significant improvement of VA and macular thickness reduction following optical coherence tomography (OCT). They have also recently published the 3-year-period follow-up in 27 eyes with a significant improvement of VA of 16.5 letters.[41] Ruiz-Moreno et al.[42] enrolled 107 highly myopic patients with CNV treated by one intravitreous injection of 1.25 mg bevacizumab. At one-year follow-up, 30 % of patients gained at least three ETDRS lines and 40 % needed re-injections. The mean number of retreatments was 0.8. An attempt to compare a single initial dose versus three consecutive monthly initial injections of bevacizumab was conducted by Ruiz-Moreno and colleagues in a prospective non-randomised study of 39 eyes.[43] Both schedules showed similar results of BCVA improvement; however, the single initial dose group required lower number of injections (1.7 versus 3.2) and much higher rate of recurrences at first-year follow-up.

It is clear from these studies reporting visual improvement with the use of anti-VEGF agents for myopic CNV that many physicians are

changing from PDT to the off-label use of anti-VEGF drugs. An attempt to compare visual outcomes from both treatments was conducted by Yoon and colleagues[44] in 142 eyes. The anti-VEGF group (both ranibizumab and bevacizumab) showed significant improvement in VA compared with the PDT alone and combinations groups. Iacono and colleagues[45] also compared both anti-VEGF treatments in a 18-month follow-up study of 55 patients on a *pro re nata* basis after the first injection. They only found greater efficacy of ranibizumab among bevacizumab in terms of number of injections administered (2.5 ranbizumab versus 4.7 bevacizumab).

## Conclusion

It is not possible to compare different studies with such variable designs and methodology, however, anti-angiogenic drugs have shown to be a safe and effective treatment option for CNV secondary to PM. In the absence of an evidence base derived from large randomised controlled clinical trials with anti-VEGF drugs, criteria for retreatment and the most effective agent for PM related CNV still remains uncertain. An advantage of ranibizumab over bevacizumab has been hypothesised: the former has a smaller molecular weight (48 kD) compared with bevacizumab (149 kD), which would allow a full and faster penetration to the retinal layers reaching the site of the CNV.[46] Moreover, ranibizumab has been stated to have a greater affinity to VEGF-A, and might have fewer potential systemic risks than bevacizumab. However, studies in rabbit eyes demonstrated a faster clearance in the vitreous cavity of ranibizumab (half-life of 2.88 days),[47] compared with bevacizumab (half-life of 4.32 days).[48]

In addition, the importance has also been suggested of the healthy RPE of these, often young, patients compared with those with AMD, allowing a better response from the treatment. This anatomic detail could be central to the understanding about the smaller amount of injections needed in these patients compared with those from AMD as reported in many of the scientific reports cited. Obviously, this trend could change with a longer follow-up. A follow-up study[49] of 71 months revealed recurrence of myopic CNV in 46.1 % of the patients after PDT or anti-VEGF injection treatment. Presence of lacquer cracks, prior PDT and absence of dark rim have been stated to be risk factors for recurrences. The results of Vadalà and colleagues are also interesting, as they consider not only new spectral-domain OCTs as the gold standard for deciding retreatment, but also symptoms such as metamorphopsia.

In summary, PDT is the only approved treatment for subfoveal CNV related to PM. Anti-angiogenic drugs have demonstrated promising results in any form and localisation of CNV, but randomised clinical trials and longer follow-up data studies are required to further determine the best modality and regimen of treatment. ■


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