Beneficial effect of anti-VEGF treatment in various rare retinal diseases

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**Keywords**  
anti-VEGF therapy, rare retinal diseases, pathological myopia, central serous chorioretinopathy

**Abstract**

**Aims:** Intravitreal application of medications allows for more effective, targeted delivery of the drug substances into the posterior pole. Anti-VEGF therapy is suitable for a wide scope of retinal disorders, especially those associated with increased VEGF release. Our purpose is to investigate the efficacy of intravitreal anti-VEGF medications outside the approved indications (AMD, RVO and DME), and to confirm that it is a beneficial treatment option for choroidal neovascularization (CNV) in various rare retinal diseases.

**Methods:** Prospective interventional study of patients with active CNV, divided into four groups according to the diagnosis was performed: group 1 – patients with pathological myopia (PM), group 2 – central serous chorioretinopathy (CSC), group 3 – dominant drusen (DD) and group 4 – pseudoxanthoma elasticum (PXE). All patients received three bevacizumab (1.25 mg) and/or aflibercept (2 mg) intravitreal injections at monthly intervals. Further treatment was administered, depending on disease activity. Baseline and monthly follow up visits included best corrected visual acuity (BCVA) measurement and full eye exam with retinal imaging.

**Results:** Sixteen patients (18 eyes) were included in the review. Group 1 (PM) consisted of 7 female (8 eyes) with mean age of 57 years and mean baseline BCVA: 0.69 logMAR. After treatment we registered improvement with increase of mean BCVA to 0.39 logMAR. In group 2 (CSC) 4 male and 1 female (5 eyes) were included, with mean age of 50 years and mean baseline BCVA: 0.17 logMAR. After treatment all patients reached visual acuity of 0.09 logMAR. Patients from the third group (DD), 1 male and 1 female (4 eyes) with mean age of 56.5 years demonstrated improvement of BCVA after treatment from 0.09 to 0.0 logMAR and from 0.39 to 0.17 logMAR, respectively. In group 4, consisting of 1 male and 1 female (2 eyes) with mean age of 46.5 years we recorded improvement of BCVA from 1.0 to 0.30 and 0.69 logMAR, respectively. Central retinal thickness decreased in all groups as a result of the treatment.

**Conclusion:** Our study confirms the hypothesis that intravitreal anti-VEGF therapy is effective both functionally and morphologically in patients with CNV secondary to varied retinal pathology such as PM, CSC, DD and PXE. This encourages us to conduct further research on anti-VEGF treatment in patients with varied retinal pathology, associated with neovascularization.

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Introduction

The use of intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents has been established as a first-line therapy for choroidal neovascularization (CNV) associated with exudative age-related macular degeneration (AMD). Although the primary focus has remained on the treatment of exudative AMD, the spectrum of diseases treated with anti-VEGF agents has quickly expanded. Vascular endothelial growth factor (VEGF)-A has been found to be a key regulator of ocular angiogenesis and vascular permeability, and is involved in the pathogenesis of several ocular diseases such as CNV secondary to AMD, diabetic macular edema (DME) and retinal vein occlusion (RVO). Based on its effectiveness in the treatment of CNV associated with exudative AMD, we decided to evaluate the effect of anti-VEGF agents on conditions, outside the registered indications, sharing pathophysiological similarities.

Patients

A prospective interventional study included 16 patients with active CNV, divided into four groups according to the diagnosis: Group 1 – Pathological myopia (PM), Group 2 – Central serous chorioretinopathy (CSC), Group 3 – Dominant drusen (DD), and Group 4 – Pseudoxanthoma elasticum (PXE).

All participating patients signed an informed consent form. The following inclusion criteria were applied:

1. PM defined as an eye with a minimum refractive er-
ror of –6 dioptres, an axial length ≥26 mm and reti-
nal signs such as lacquer cracks, active subfoveal
CNV confirmed with FA and OCT.

2. Chronic central serous chorioretinopathy (CSC)
characterized by long-standing (more than 6
months) serous neurosensory detachment.

3. DD-patients with drusen that are usually numerous
and of varying size, typically extending beyond the
vascular arcades and nasal to the optic disc

4. PXE patients with characteristic clinical findings on oph-
thalmoscopy and fluorescein angiography (FA), as well as
general systemic characteristics of PXE. The diagnosis was
confirmed histopathologically by biopsy of the skin lesions.

5. An active macular CNV.

Exclusion criteria encompassed other retinal vascular
diseases, ocular surgery or intravitreal anti-VEGF ther-
apy less than 6 months before starting treatment, un-
controlled glaucoma or ocular inflammation.

Table 2. Central serous chorioretinopathy (CSC). M-male, F-female, R-right eye, L-left eye, CNV-choroidal neovascular mem-
brane

<table>
<thead>
<tr>
<th>Patient No, sex, age/years</th>
<th>R/L</th>
<th>Duration (months)</th>
<th>CNV</th>
<th>BCVA</th>
<th>Foveal thickness (µm)</th>
<th>Change of fluorescein leakage</th>
<th>Follow up months</th>
<th>Number of injections</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Baseline</td>
<td>Final</td>
<td>Baseline</td>
<td>Final</td>
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<tr>
<td>1/M/53</td>
<td>L</td>
<td>12</td>
<td>Foveal</td>
<td>0.6</td>
<td>1.0</td>
<td>179</td>
<td>139</td>
<td>Reduced</td>
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<tr>
<td>2/M/48</td>
<td>R</td>
<td>12</td>
<td>Juxtafoveal</td>
<td>0.4</td>
<td>0.8</td>
<td>264</td>
<td>138</td>
<td>Reduced</td>
</tr>
<tr>
<td>3/M/55</td>
<td>R</td>
<td>8</td>
<td>Foveal</td>
<td>0.8</td>
<td>1.0</td>
<td>293</td>
<td>190</td>
<td>Reduced</td>
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<tr>
<td>4/M/50</td>
<td>L</td>
<td>11</td>
<td>No</td>
<td>0.9</td>
<td>1.0</td>
<td>208</td>
<td>194</td>
<td>Unchanged</td>
</tr>
<tr>
<td>5/F/44</td>
<td>L</td>
<td>12</td>
<td>No</td>
<td>0.8</td>
<td>1.0</td>
<td>263</td>
<td>178</td>
<td>Reduced</td>
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</tbody>
</table>

Table 3. Dominant drusen (DD) and pseudoxanthoma elasticum (PXE)

<table>
<thead>
<tr>
<th>Patient No, sex, age/years</th>
<th>R/L</th>
<th>Diagnosis</th>
<th>CNV</th>
<th>BCVA</th>
<th>Foveal thickness (µm)</th>
<th>Change of fluorescein leakage</th>
<th>FAF</th>
<th>Follow up (months)</th>
<th>Number of injections</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Baseline</td>
<td>Final</td>
<td>Baseline</td>
<td>Final</td>
<td></td>
</tr>
<tr>
<td>1/F/59</td>
<td>R</td>
<td>DD</td>
<td>Foveal</td>
<td>0.4</td>
<td>0.7</td>
<td>384</td>
<td>172</td>
<td>Reduced</td>
<td>Unchanged</td>
</tr>
<tr>
<td>2/M/55</td>
<td>R</td>
<td>DD</td>
<td>Juxtafoveal</td>
<td>0.8</td>
<td>1.0</td>
<td>220</td>
<td>218</td>
<td>Reduced</td>
<td>Unchanged</td>
</tr>
<tr>
<td>3/M/35</td>
<td>L</td>
<td>PXE</td>
<td>Juxtafoveal</td>
<td>0.1</td>
<td>0.4</td>
<td>239</td>
<td>204</td>
<td>Reduced</td>
<td>Increased</td>
</tr>
<tr>
<td>4/F/58</td>
<td>L</td>
<td>PXE</td>
<td>Foveal</td>
<td>0.1</td>
<td>0.2</td>
<td>309</td>
<td>281</td>
<td>Reduced</td>
<td>Increased</td>
</tr>
</tbody>
</table>

Figure 2. Neurosensory detachment and small foveal CNV (A) before treatment and (D) after treatment with three intravitreal
injections of Bevacizumab. (E) FA in the late phase (3 min) demonstrating decreased leakage from CNV one month after the last
injection. (C) Horizontal OCT image before treatment – shallow neurosensory detachment (F) OCT image 1 month after the last
intravitreal injection shows complete resolution of subretinal fluid.
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Figure 3. (A) Fundus images of Patient 1 showing dominant drusen (DD) and small subretinal hemorrhage adjacent to subfoveal CNV. (D) After treatment with 3 intravitreal applications of Aflibercept no subretinal hemorrhage is present. (B) FA in the late phase (3 min) showing moderate leakage from the CNV before treatment. (E) FA in the late phase (3 min) demonstrating decreased leakage from CNV one month after the last injection. (C) and (F) On FAF preexisting atrophic areas remain of similar size. (G) Horizontal OCT image before treatment showing intraretinal cystic spaces, small CNV and adjacent neurosensory detachment. Central foveal thickness is 384 µm. (H) Complete resolution of intraretinal and subretinal fluid after treatment. Central thickness is 171 µm.

Methods
The patients received three intravitreal bevacizumab (1.25 mg) and/or aflibercept (2 mg) injections at monthly intervals. Further treatment was administered, depending on disease activity. Baseline and monthly follow-up visits included distance best-corrected visual acuity (BCVA) measurements, complete ophthalmic examination, including slit-lamp biomicroscopy, colour fundus photography, fundus autofluorescence (FAF), digital fluorescein angiography (FA), (Carl Zeiss Meditec GmbH, Jena, Germany) and optical coherence tomography (OCT) scanning (Stratus OCT, Zeiss Meditec, Dublin, CA). The primary endpoint was BCVA and central macular thickness (CMT) 1 month after the last treatment compared to baseline.

Results
Sixteen patients (18 eyes) were included in the study. GROUP 1 (PM): 7 female (8 eyes) with mean age – 57 (49-70) years, mean spherical equivalent refraction: –9.75 (range: –7.0–12.0) D and mean follow-up 8.5 (range: 2–14) months were included. Mean BCVA before treatment was 0.69 logMAR. After treatment we registered improvement with increase of mean BCVA to 0.39 logMAR. BCVA remained unchanged in one patient (12.5%). Mean central macular thickness before treatment was 239 (range: 173–322) µm and 197 (range: 237–151) µm after treatment. Retinal thickness reduced in 6 of 8 eyes (75%) and remained the same in 2 of 8 eyes (25%). Fluorescein angiography showed reduced leakage in 5 of 7 eyes (71.5%) and did not change in 2 of 7 eyes (28.5%).

GROUP 2 (CSC): Five patients (5 eyes), four males (80%) and one female (20%), with mean age 50 (44-55) years were included. Mean duration of symptoms was 11 (8-12)months, mean baseline BCVA 0.17 logMAR and mean BCVA 0.09 logMAR after treatment. Mean OCT thickness within the central region decreased from 241 (293-179) µm to 168 (194-138) µm. Based on FA four eyes (80%) had CNV. Leakage from active CNVs decreased after treatment in 4 eyes (80%) and did not change in one eye (20%).
GROUP 3 Dominant Drusen (DD): 1 female and 1 male patient (2 eyes) with:

<table>
<thead>
<tr>
<th>BCVA:</th>
<th>Before treatment</th>
<th>After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>0.39 logMAR</td>
<td>0.17 logMAR</td>
</tr>
<tr>
<td>Patient 2</td>
<td>0.09 logMAR</td>
<td>0.00 logMAR</td>
</tr>
</tbody>
</table>

Central foveal thickness of patient 1 decreased from 384 µm to 171 µm, while patient 2 had no change. Based on early frames of FA patient 1 had foveal and patient 2 juxtafoveal CNV. Leakage from active CNV decreased after treatment with aflibercept of patient 1. Patient 2 had no change of fluorescein leakage of the CNV after three applications of bevacizumab and was switched to aflibercept. After three applications central leakage disappeared.

GROUP 4 Pseudoxanthoma Elasticum: 1 male and 1 female (2 eyes) with mean baseline BCVA: 1 logMAR. Both patients had CNV adjacent to preexisting fibrotic scars. After treatment we recorded improvement of BCVA to 0.30 logMAR of patient 1 and to 0.69 logMAR of patient 2. Leakage of CNV subsided and OCT thickness decreased: Patient 1: from 239 to 204 µm, and Patient 2: from 309 to 281 µm.

Discussion

In our study an improvement of visual acuity was observed, central OCT thickness decreased and fluorescein leakage regressed in all groups. Successful results indicate that VEGF has an important role in CNV secondary to PM, CSC, DD and PXE. Limitations of the study include: short follow up period, small number of patients and different medications used. The group with PM demonstrated very good results with decrease of CNV activity after a relatively small number of injections (3.5 on average). Morphological and functional results were stable for a long follow up period without need of retreatment. Similar results of anti-VEGF treatment for myopic CNV have been previously reported (1, 2). Yamamoto et al (2) published a retrospective case series of 11 eyes with pathological myopia of nine patients injected with intravitreal bevacizumab (1.25 mg). After a mean follow-up of 153 days, there was a mean visual acuity improvement of 3.5 lines and a mean OCT foveal thickness reduction of 103 µm with no adverse events.

Anti-VEGF agents are not considered first-line treatment for either acute or chronic CSC, but several
small trials have demonstrated good results. Although VEGF levels are not elevated in aqueous samples from CSC eyes, some have hypothesized that hypoxic conditions in the choroid or RPE could lead to compartmentalized VEGF expression not detected in aqueous samples (4, 5). Chan and al 6 reported prospective study of 15 patients (15 eyes) with CNV secondary to CSC. Their results demonstrated that three monthly injections of intravitreal bevacizumab resulted in complete regression of CNV with no angiographic leakage in all eyes at three months post treatment. In our study we observed regression of CNV leakage and desorption of the subretinal fluid after three monthly injections.

Effectiveness of bevacizumab in CNV in PXE has been demonstrated in different studies (7). Finger et al. (8, 9) published the results of a study of 14 patients with CNV secondary to PXE treated with bevacizumab (1.5 mg) at monthly intervals. BCVA improved significantly especially in patients with early disease. In our study visual acuity also improved, despite the advanced stage of PXE.

Small case series of patients with CNV secondary to Familial (dominant) drusen treated with bevacizumab has been reported in the literature. Similarly to our results, Sohn at al. 10 reported three cases treated with intravitreal bevacizumab, which showed good morphologic and functional outcome.

**Conclusion**

Our study confirms the hypothesis that intravitreal anti-VEGF therapy is effective both functionally and morphologically in patients with CNV secondary to varied retinal pathology such as PM, CSC, DD and PXE. This encourages us to conduct further research on anti-VEGF treatment in patients with retinal pathology, associated with neovascularization.

**References**


