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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) mesurement 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 1female (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-

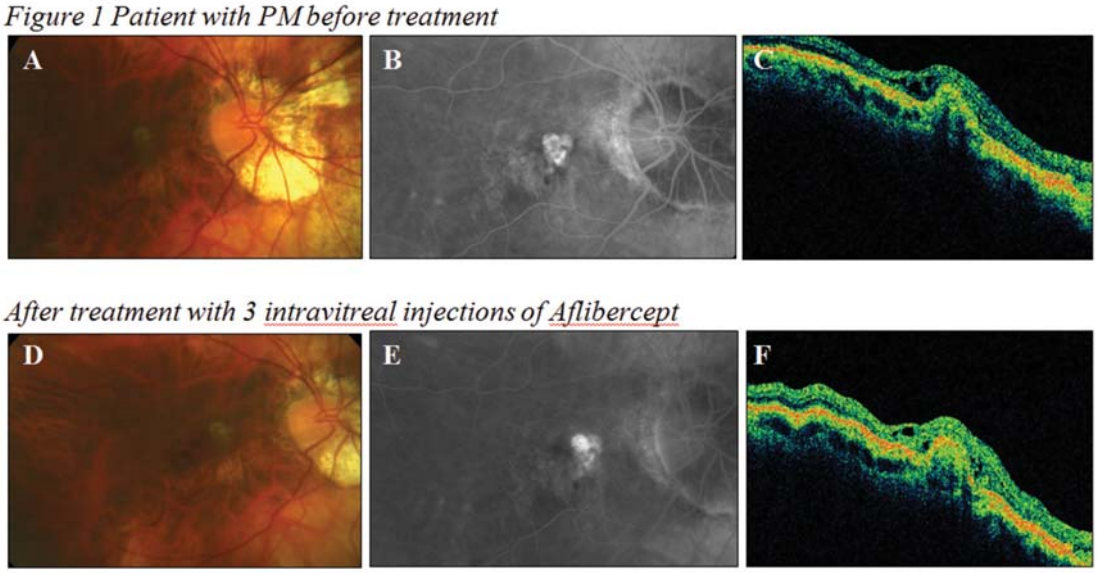

Figure 1. Patient 6 (A) Fundus photograph showing subfoveal CNV before treatment and (D) after treatment. (B) Fluorescein angiography in the late phase (5 min) showing leakage from the CNV before treatment. (E) FA in the late phase (5 min) showing decreased leakage from CNV 2 months after 3 intravitreal injections of Aflibercept. (C) Horizontal optical coherence tomography (OCT) image before treatment showing a hyper-reflective lesion under the retina that corresponds to the CNV with overlying intraretinal fluid. The thickness of the fovea is 180µm. (F) OCT image 2 months after the last intravitreal injection showing decreased intraretinal fluid. The thickness of the foveal retina is 151 µm.

Table 1. Pathological myopia (PM)

Patient No, sex, age/years	R/L	Refraction (D)	Position of CNV	BCVA		Foveal thickness (µm)		Change of fluorescein leakage	Follow up (months)	Number of injections
				Baseline	Final	Baseline	Final			
1/F/70	L	–7.0	Foveal	0.1	0.3	322	208	Reduced	9	3
2/F/56	L	–11.0	Juxtafoveal	0.4	0.7	185	179	Not done*	4	3
3/F/58	R	–12.0	Foveal	0.1	0.2	173	161	Unchanged	2	2
4/F/55	L	–8.0	Foveal	0.05	0.05	272	235	Unchanged	12	3
5/F/50	R	–9.0	Foveal	0.4	1.0	180	151	Reduced	14	3
	L	–10.0	Foveal	0.05	0.1	276	227	Reduced	14	3
6/F/49	R	–10.0	Foveal	0.3	0.7	237	180	Reduced	7	3
7/F/64	R	–11.0	Juxtafoveal	0.1	0.3	269	237	Reduced	6	5

F-female, R-right, L-left, D-diopters, Refraction-spherical equivalent refraction , *allergy

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

Patient No, sex, age/years	R/L	Duration (months)	CNV	BCVA	Foveal thickness (μm)		Change of fluorescein leakage		Follow up months	Number of injections
					Baseline	Final	Baseline	Final		
1/M/53	L	12	Foveal	0.6	1.0	179	139	Reduced	9	3
2/M/48	R	12	Juxtafoveal	0.4	0.8	264	138	Reduced	5	3
3/M/55	R	8	Foveal	0.8	1.0	293	190	Reduced	4	1
4/M/50	L	11	No	0.9	1.0	208	194	Unchanged	10	3
5/F/44	L	12	No	0.8	1.0	263	178	Reduced	8	3

ror of –6 dioptres, an axial length ≥26 mm and retinal 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 ophthalmoscopy and fluorescein angiography (FA), as well as general systemic characteristics of PXE. The diagnosis was confirmed histopathologicaly by biopsy of the skin lesions.
5. An active macular CNV.

Exclusion criteria encompassed other retinal vascular diseases; ocular surgery or intravitreal anti-VEGF therapy less than 6 months before starting treatment, uncontrolled glaucoma or ocular inflammation.

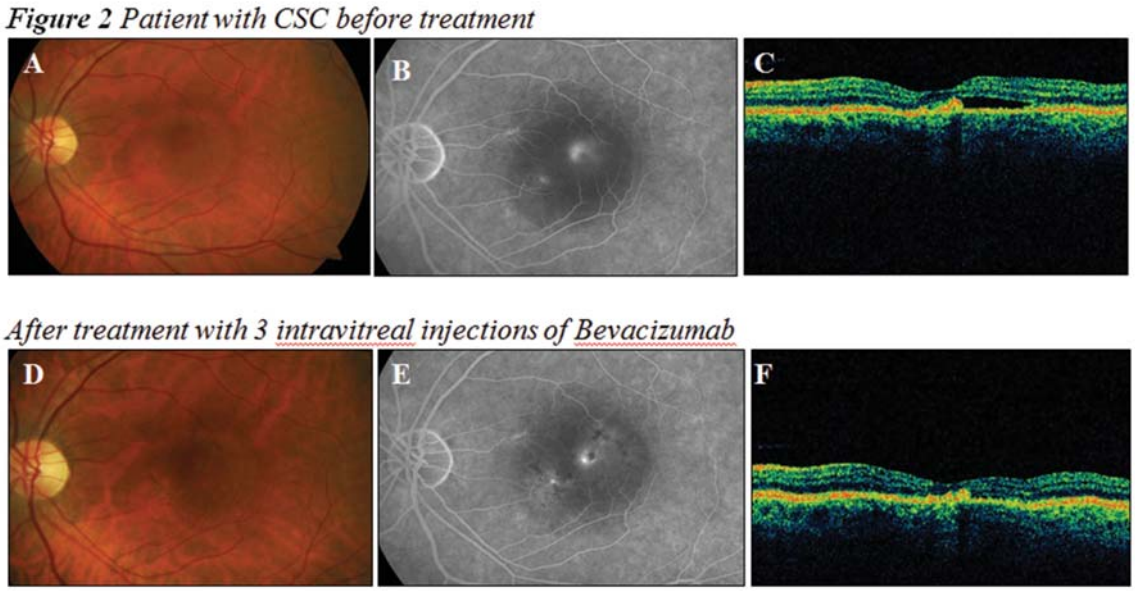

Figure 2. Neurosensory detachment and small foveal CNV (A) before treatment and (D) after treatment with three intravitreal injections of Bevacizumab. (E) FA in the late phase (3 min) demonstrating decreased leakage from CNV one month after the last injection. (C) Horizontal OCT image before treatment -shallow neurosensory detachment (F) OCT image 1 month after the last intravitreal injection shows complete resolution of subretinal fluid.

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

Patient No, sex, age/years	R/L	Diagnosis	CNV	BCVA	Foveal thickness (μm)		Change of fluorescein leakage		FAF	Follow up (months)	Number of injections
					Baseline	Final	Baseline	Final			
1/F/59	R	DD	Foveal	0.4	0.7	384	172	Reduced	Unchanged	8	3
2/M/55	R	DD	Juxtafoveal	0.8	1.0	220	218	Reduced	Unchanged	10	6
3/M/35	L	PXE	Juxtafoveal	0.1	0.4	239	204	Reduced	Increased	14	9
4/F/58	L	PXE	Foveal	0.1	0.2	309	281	Reduced	Increased	6	3

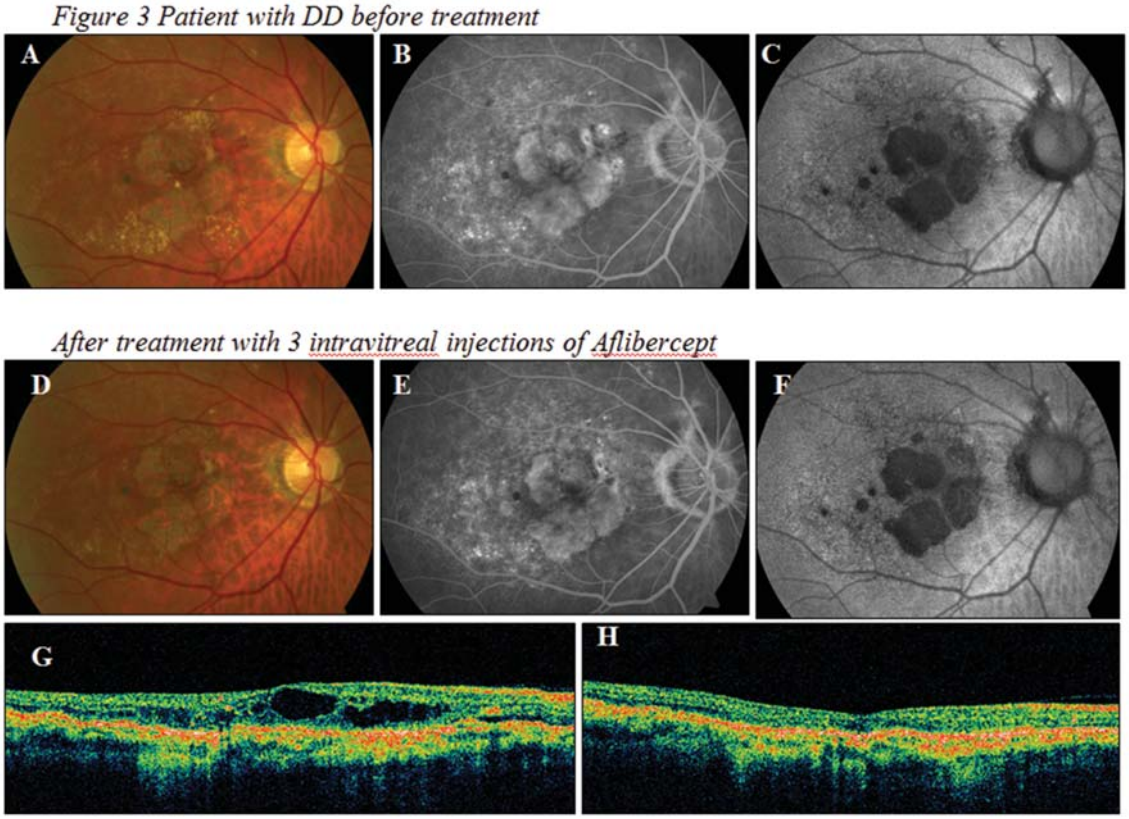

Figure 3. (A) Fundus images of Patient 1 showing dominant drusen (DD) and small subretinal hemorrhage adjascent to subfoveal CNV. (D) After treatment with 3 intravitreal applications of Aflibercept no subretinal hemorrhage is present. (B)FA in the late phase (3 min) showing moderate leakage from the 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%).

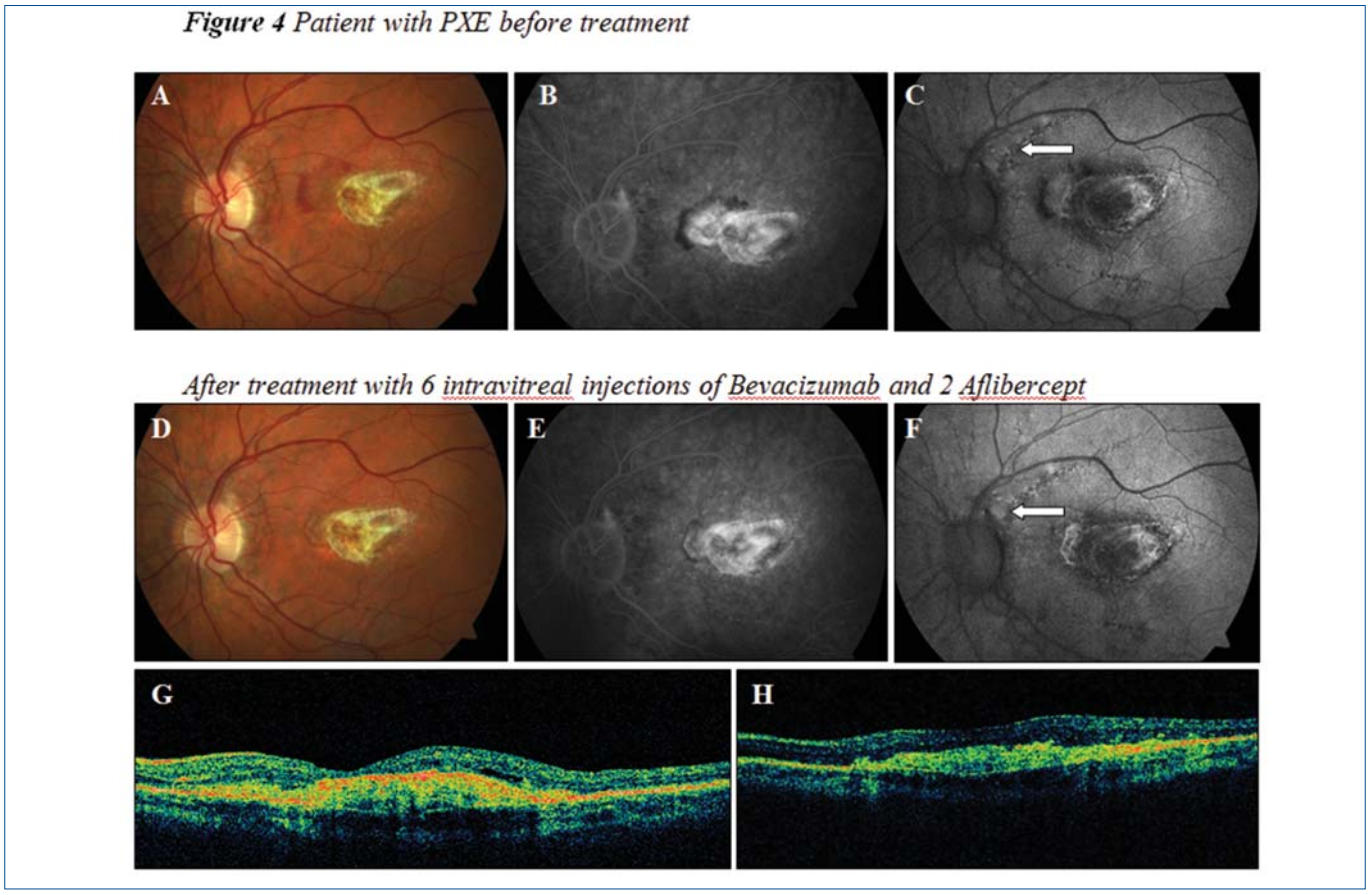

Figure 4. (A) Fundus image of patient 1 with PXE showing angioid streaks, subfoveal fibrotic tissue and adjascent CNV with small surrounding subretinal hemorrhage. (B) After treatment with six intravitreal applications of Bevacisumab and two of Aflibercept. (B) FA shows leakage from juxtafoveal CNV and staining of fibrotic tissue. (E) Leakage disappears and is replaced by fibrotic staining after treatment. (C) and (F) On FAF preexisting atrophic areas enlarge over the CNV. Pattern dystrophy-like changes are present (white arrows). (H) OCT shows reduction of subretinal fibrosis and intraretinal fluid.

GROUP 3 Dominant Drusen (DD): 1 female and 1 male patient (2 eyes) with:

BCVA:	Before treatment	After treatment
Patient 1	0.39 logMAR	0.17 logMAR
Patient 2	0.09 logMAR	0.0 logMAR

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.

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