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Authors: Kowalczuk L, Matet A, Dirani A, Daruich A, Ambresin A, Mantel I, Spaide RF, Turck N, Behar-Cohen F

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Title: Efficacy of intravitreal aflibercept in macular telangiectasia type 1 is linked to the ocular angiogenic profile

Abbreviated title: Aflibercept for MacTel type 1

Laura Kowalczuk PhD [1*], Alexandre Matet MD[1*], Ali Dirani MD[1], Alejandra Daruich MD[1], Aude Ambresin MD[1], Irmela Mantel MD[1], Richard F. Spaide MD[2], Natacha Turck PhD[3], Francine Behar-Cohen MD-PhD[1]

[1] University of Lausanne, Department of Ophthalmology, Fondation Asile des Aveugles, Jules-Gonin Eye Hospital, Lausanne, Switzerland

[2] Vitreous, Retina, Macula Consultants of New York and the LuEsther T. Mertz Retina Research Center, Manhattan Eye, Ear and Throat Hospital, New York, USA

[3] University of Geneva, Department of Human Protein Science, Geneva, Switzerland

* Both authors have contributed equally to the work

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Corresponding Author: Francine Behar-Cohen
Jules-Gonin Eye Hospital
Avenue de France 15, CP 133; CH-1000 Lausanne 7, Switzerland
Phone: +41-21 626 80 86; Fax: +41-21 626 85 96
Email: francine.behar@gmail.com

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Key words: Aflibercept, Macular telangiectasia, Retina

Summary statement: In this interventional case series, eight patients presenting macular telangiectasia type 1 with macular edema were treated by intravitreal aflibercept. The favorable clinical response observed with this treatment is consistent with the profile of angiogenic factors analyzed in their aqueous humors.

ABSTRACT

Purpose: To evaluate intravitreal aflibercept in macular telangiectasia type 1 (MacTel1) patients and measure their ocular angiogenic profile.

Methods: Eight subjects with MacTel1 refractory to bevacizumab, ranibizumab or laser therapy, and switched to aflibercept, were included. Best-corrected visual acuity (BCVA), central macular thickness (CMT), and cystic areas quantified on optical coherence tomography B-scans were assessed during 12 months. Perifoveal capillary densities were measured on OCT angiography. Aqueous humor was sampled from 6 patients and 8 controls undergoing cataract extraction. Growth factors were quantified using a multi-array immunoassay.

Results: Over 12 months, patients received 6.6 ± 1.4 (range, 5-8) intravitreal aflibercept injections. Twelve months after switching to aflibercept, BCVA increased by ≥5 letters in n=5/8 patients, compared to pre-aflibercept levels. Mean BCVA improved from 79.6 (~20/50) to 88.0 (~20/35) ETDRS letters (*P*=0.042) and CMT decreased from 434±98 to 293±59 µm (*P*=0.014). Compared to controls, the profile of angiogenic factors in MacTel1 eyes revealed no difference in VEGF-A levels, but significantly higher levels of PlGF (*P*=0.029), soluble VEGF-receptor-1 (sFlt-1; *P*=0.013), VEGF-D (*P*=0.050) and Tie-2 (*P*=0.019). PlGF levels were inversely correlated to both superficial and deep capillary plexus densities on OCT angiography (*P*=0.03).

Conclusion: The clinical response to aflibercept coupled to the angiogenic profile of MacTel1 eyes support the implication of the PlGF/Flt-1 pathway in MacTel1.

INTRODUCTION

"Idiopathic juxtafoveal telangiectasia" is a generic term that encompasses different clinical entities first classified by Gass and Oyakawa in 1982,[1] then by Gass and Blodi in 1993.[1] In 2006, Yannuzzi *et al.*[2] proposed a simplified classification under the term "idiopathic macular telangiectasia", with two distinct types: type 1, "aneurysmal telangiectasia" and type 2, "perifoveal telangiectasia", also known as MacTel. These classifications are based on clinical features, as no specific molecular signature or pathogenic mechanisms have yet been identified.

Idiopathic macular telangiectasia type 1 (MacTel 1) is usually unilateral and affects mostly men of 40-50 years of age at presentation.[1] Microvascular ectasia and increased tortuosity of the macular capillary network are visible on fundus examination, may extend to the temporal side of the macula over an area of two-disc diameter or greater,[1,2] and may be associated to peripheral vascular changes.[3] Telangiectasia frequently causes macular edema with lipid exudates of variable severity, and subsequent vision loss. Location, morphology and degree of leakage of the microvascular ectasia, as well as capillary non-perfusion are best identified on fluorescein angiography.

Whether MacTel 1 is a milder, later and more central form of Coats' disease is debated, since both entities associate vascular telangiectasia with aggressive exudation, unilateral involvement and male predominance.[3,5] To confirm the diagnosis of MacTel 1, disorders causing secondary telangiectasia must be excluded, which included retinal vein occlusion, diabetic retinopathy, ocular ischemic syndrome, hypertensive retinopathy and more rarely posterior segment inflammation, radiation maculopathy, sickle-cell maculopathy or localized retinal capillary hemangioma.

MacTel 1 is a rare disease and there is no consensus regarding treatment schemes. Laser photocoagulation can be performed on accessible ischemic areas but may also target leaky aneurysms. Intravitreal anti-vascular endothelial growth factor (VEGF) therapy has also been assessed, with inconstant results. Although bevacizumab[6,7] and ranibizumab[8,9] showed some efficacy in reducing macular edema and improving vision, three case series reported that only a minority of patients responded favorably to intravitreal bevacizumab.[10,11,12] Recently, three groups reported that MacTel 1 patients may be non-responders or become refractory to bevacizumab[13,14,15] or ranibizumab,[15] including two case reports describing a favorable response after switching to intravitreal aflibercept.[14,15] Aflibercept is a soluble decoy receptor that associates an immunoglobulin backbone to extracellular sequences of the VEGF receptors VEGFR-1 (also called Flt-1) and VEGFR-2. In contrast to specific anti-VEGF antibodies such as bevacizumab and ranibizumab, which bind to the VEGF-A isoform only, aflibercept also blocks another ligand of Flt-1, placental growth factor (PlGF). Through its binding to Flt-1, PlGF is suspected to enhance vascular permeability and to amplify the effects of VEGF on pathological angiogenesis.[16] PlGF has been implicated in the resistance to anti-VEGF treatments in patients with malignant tumors[17,18] and various retinal diseases, including diabetic macular edema.[19,20] Aflibercept may overcome this hurdle by neutralizing PlGF along with VEGF.[21,22] Interestingly, in an adult rat model, the overexpression of rat PlGF did not induce pre-retinal neovessels, as observed when VEGF is overexpressed,[23] but produced retinal vessel abnormalization manifested by tortuosity, dilation and capillary aneurysms,[24] suggesting a potential role of PlGF in the pathogenesis of aneurysmal telangiectasia.

In this context, the aim of this study was to retrospectively evaluate the effect of intravitreal aflibercept therapy in patients with macular edema caused by MacTel 1, and to correlate it to the profile of angiogenic factors in aqueous humor.

METHODS

Subjects

This retrospective interventional case series involving eight human subjects and eight healthy controls adhered to the tenets of the Declaration of Helsinki. The protocol was approved by the local Ethics Committee of the Swiss Department of Health on research involving human subjects (CER-VD N°95/15 and 340/15) and by an Institutional Review Board from Western Institutional Review Board (Puyallup, Washington). All patients signed an informed consent form before aqueous humor sampling. Six consecutive patients followed from December 2013 to July 2015at Jules-Gonin Eye Hospital (Lausanne, Switzerland), and two consecutive patients followed at the Vitreous, Retina, Macula Consultants of New York (New York, USA) were included in this study. Inclusion criteria were: 1) macular edema due to idiopathic MacTel 1 without medical or ophthalmological history suggesting secondary macular telangiectasia, and 2) persistence of macular edema following a well-conducted treatment by retina specialists with intravitreal bevacizumab (Avastin; Genentech, Inc., South San Francisco, CA, USA), ranibizumab (Lucentis; Novartis Pharma AG, Basel, Switzerland and Genentech, Inc., South San Francisco, CA, USA) and/or laser photocoagulation, justifying a treatment switch to intravitreal aflibercept (Eylea; Bayer, Leverkusen, Germany).

Eight sex- and age-matched patients undergoing cataract surgery and having no history of diabetes or retinal disease were included during the same period as control subjects for aqueous humor sampling.

Patient treatment and follow-up

Following two initial monthly loading doses, patients received intravitreal aflibercept on a pro re nata (as needed) regimen. Decision for re-injection was made by two retina specialists (RFS or FBC), and re-injections were performed at intervals of 4 weeks or more. They were indicated in case of persistent or recurrent macular edema manifesting by intraretinal cysts and/or subretinal fluid.

At all visits, best-corrected visual acuity was measured using an Early Treatment Diabetic Retinopathy Study (EDTRS) chart, and serial Spectral-Domain Optical Coherence Tomography (SD-OCT) images on Spectralis (Heidelberg Engineering, Heidelberg, Germany) were obtained. Confocal fluorescein and indocyanine green angiography on Spectralis had been performed in all cases at presentation for the diagnosis of MacTel 1 and were repeated at the discretion of the treating retina specialist. Optical coherence tomography angiography (OCTA) images were acquired using the Angiovue RTx 100, based on the AngioVue Imaging System (Optovue, Inc., Freemont, CA).

Clinical charts were retrospectively reviewed, and data were recorded at baseline (corresponding to the last visit before the first intravitreal aflibercept injection) and one, three, six and twelve months after baseline.

Spectral-domain optical coherence tomography imaging and quantification of intraretinal cysts area

At each time point, high-quality 30° horizontal single B-scans SD-OCT and 20°×20° 97-section horizontal grids were acquired using the follow-up mode on Spectralis. The central macular thickness (CMT) was automatically measured in the central subfield of an ETDRS grid on the built-in software. For graphical purposes, the boundaries of the cystoid edema regions were outlined with a red contour and superimposed over the original SD-OCT images, using a custom semi-automated algorithm on Matlab (Version R2015b, Mathworks, Natick, MA, USA) detailed in the supplemental Figure.

Optical coherence tomography angiography imaging and macular capillary density

The optical coherence tomography angiography Angiovue RTx 100 instrument was used to obtain amplitude decorrelation angiography images. This instrument has an A-scan rate of 70,000 scans per second, using a light source centered on 840 nm and a bandwidth of 50 nm. Each OCTA volume contains 304 x 304 A-scans with two consecutive B-scans captured at each fixed position before proceeding to the next sampling location. Split-spectrum amplitude-decorrelation angiography was used to extract the OCTA information. Each OCTA volume is acquired in 3 seconds and two orthogonal OCTA volumes are acquired in order to perform motion correction. Angiography information displayed is the average of the decorrelation values when viewed perpendicularly through the thickness being evaluated.

In order to obtain comparable 3×3-mm OCTA scans between subjects, volumes were automatically segmented by the built-in software to provide images of the superficial plexus (3 µm below the inner limiting membrane to 16 µm below the outer border of the inner plexiform layer) and deep plexus (16-69 µm below the outer border of the inner plexiform layer). The correct segmentation for each patient was controlled before reporting the capillary densities calculated using the AngioVue software.

Aqueous humor sampling

At the time of an aflibercept intravitreal injection indicated for macular edema, 50-150 µL of aqueous humor were sampled by anterior chamber tap before the injection, using a 30-Gauge needle and a 1-mL syringe, and immediately frozen at -80°C. Before aqueous humor sampling, a time lapse of at least 7 weeks from the previous anti-VEGF injection (ranibizumab, bevacizumab or aflibercept) was observed in all patients. Given that pharmacological observations[25,26,27] and mathematical models[28] have estimated the vitreous elimination half-life ($t_{1/2}$) of ranibizumab, bevacizumab and aflibercept to be respectively $t_{1/2}$=3.2-7.2 days, $t_{1/2}$= 4.9-5.6 days, and $t_{1/2}$=4.6-4.8 days,[25-28] aqueous sampling was performed when no residual anti-VEGF drug remained in the vitreous, after a clearance time ≥ $7 \times t_{1/2}$. In the control group, the anterior chamber tap was performed at the beginning of cataract surgery before any fluid was injected into the anterior chamber.

Angiogenic factor levels in aqueous humors

Aqueous humor levels of soluble VEGFR-1 (sFlt-1), PlGF, the tyrosine kinase receptor Tie-2 with immunoglobulin-2 and EGF-like domains (Tie-2), VEGF-A_{165}, VEGF-C, VEGF-D, and basic Fibroblast Growth Factor (bFGF) were measured, on the same plate, using a multi-array high-sensitive immunoassay (V-PLex Angiogenesis Panel 1 Kit; Meso Scale Discovery, Rockville, MD, USA). This standardized kit was used according to the manufacturer's instructions. Standard curves for each angiogenic factor were generated with the provided calibration kit and the samples were assayed in duplicate, without dilution. Data acquisition and analysis were performed with the Meso Scale reader (MSD Quickplex SQ-120, Meso Scale Diagnostics, Rockville, MD, USA) and its dedicated software (Discovery Benchmark version 4.0.12). Detection thresholds for all angiogenic factors were set between 1 and 20 pg/mL and coefficients of variation were inferior to 10%.

Statistical analysis

Results were expressed as mean ± standard deviation (SD). Biological and clinical analyses were carried out on GraphPad Prism 5 (GraphPad Software Inc., La Jolla, CA, USA). The nonparametric Mann-Whitney U-test and Wilcoxon paired test were used to compare data, when applicable. Spearman correlation was used to evaluate relationships between angiogenic factors levels and clinical parameters. A two-tailed P-value<0.05 was considered statistically significant.

RESULTS

Patient characteristics

Eight patients with MacTel 1, seven male and one female, with a mean age of 63.0±10.3 years (range, 45-74 years) were included in this study. Clinical characteristics, previous treatments, and number of intravitreal aflibercept injections are reported in Table 1. All patients had been previously treated with extra-macular and/or macular laser photocoagulation, combined with intravitreal anti-VEGF therapy in 7 patients. Four patients had received bevacizumab, two patients had received ranibizumab, and one patient had received sequentially bevacizumab, ranibizumab and dexamethasone implant. Following an optimal treatment regimen with these therapies the patients had a mean central macular thickness of 434 ± 98 µm. Over the 12-month study period, they received 6.6 ± 1.4 intravitreal aflibercept injections (range, 5-8).

Effect of intravitreal aflibercept therapy

A clinical illustration of a patient refractory to bevacizumab therapy and responsive to aflibercept therapy is provided in Figure 1 (Case 4). Figure 2 shows the baseline and 12-month SD-OCT B-scans and corresponding thickness maps from the eight patients included in this study, demonstrating the clinical response to aflibercept treatment.

The anatomical and visual outcomes of intravitreal aflibercept therapy by 12 months are summarized in Table 2. The CMT decreased in all patients, with a significant reduction from 434 ± 98 µm to 293 ± 59 µm (*P*=0.014). The best-corrected visual acuity improved in 7 out of 8 patients with a mean significant improvement from 79.6 ± 16.3 (~20/52) to 88.0 ± 11.2 (~20/35) ETDRS letters (*P* =0.042). There was an improvement by 5 or more ETDRS letters in 5 out of 8 patients. Both anatomical and visual parameters improved progressively over time, as illustrated in Figure 3. After one intravitreal aflibercept injection, a reduction in central macular thickness was observed in all patients, with a significant reduction as compared to baseline (308.6 ± 32.9 µm, *P*=0.016), that was maintained over the 12-month follow-up. By month 6, visual acuity levels were significantly improved (88.0 ± 11.3 letters (~20/35), *P*=0.02), which was maintained at the 12-month time point.

Angiogenic factor levels in aqueous humor

The eight individuals selected for the control group of aqueous humor analysis were male with a mean age of 68 ± 12 years old (range, 50-85), not significantly different from the six subjects with MacTel 1 from whom aqueous humor was sampled (Cases 1 to 6, mean age: 61 ± 11 years, *P*=0.40).

The profiles of angiogenic factors in the aqueous humor of patients with MacTel 1, compared to healthy controls, are represented in Figure 4. There was no difference in VEGF-A levels (×1.3, *P*=0.95), but significantly higher levels of sFlt-1 (×4.3, *P*=0.013), PlGF (×2.2, *P*=0.029), as well as Tie-2 (×3.7, *P*=0.019) and VEGF-D (×6.8, *P*=0.049). VEGF-C and bFGF levels were higher without reaching statistical significance. Mean aqueous levels of angiogenic factors in affected and control subjects are reported in the Table 3.

Correlations between imaging and biological parameters

OCTA scans were analyzed to determine the perifoveal capillary densities in the superficial and deep capillary plexuses. Figure 5 provides an illustration of multimodal imaging in one patient (Case 1), with OCTA of the superficial and deep capillary plexuses, and the corresponding capillary density maps.

An exhaustive account of the functional and anatomical parameters, as well as aqueous levels of angiogenic factors is given in the Supplemental Table 1. When exploring possible correlations between these parameters (Supplemental Table 2), we found a significant, inverse correlation between the perifoveal capillary density of both superficial and deep capillary plexuses on OCTA, and aqueous levels of PlGF (*P*=0.03, *r*=-0.89).

DISCUSSION

In this case series of 8 patients with MacTel 1, treatment by intravitreal aflibercept, that blocks both VEGF-A and PlGF, showed significant anatomical and functional effects on macular edema. Anatomical improvement was observed after one intravitreal injection of aflibercept in all cases, including those incompletely responsive to other anti-VEGF therapies that do not inhibit the PlGF-mediated Flt1 pathway. These results are supported by measurements of higher levels of PlGF, but not VEGF-A, in the aqueous humor of patients with MacTel 1 compared to healthy controls.

There are to date two case reports on the effects of intravitreal aflibercept in MacTel 1. Shibeeb *et al*.[14] described the complete resolution of macular edema and visual improvement after 4 aflibercept injections in one MacTel 1 case refractory to 3 monthly bevacizumab injections, and to laser photocoagulation. Recently, Kovach *et al*.[15] reported the beneficial effect over 3 years of aflibercept therapy on macular edema secondary to MacTel1 in one patient previously non-responding to 6 monthly bevacizumab, 7 monthly ranibizumab, and 3 triamcinolone acetonide injections. These findings are consistent with our observations. Before the intravitreal formulation of aflibercept became available for retina specialists, several investigators had evaluated the intravitreal anti-VEGF antibodies bevacizumab and ranibizumab in type 1- and type 2- idiopathic macular telangiectasia, with limited outcomes. Noticeably, the exact role of VEGF in the development of primary telangiectasia is not clear, and intra-ocular VEGF levels in type 1 or type 2 idiopathic macular telangiectasia had not been reported before the present study. Two case reports have suggested a favorable effect of intravitreal bevacizumab on MacTel 1,[6,7] but these observations were not confirmed by three small case series. Matsumoto and Yuzawa reported 4 patients with MacTel 1 who received 3 to 4 intravitreal bevacizumab injections, over a 6-month period. The microaneurysms regressed in one of the four eyes, but visual acuity did not improve in any of the patients.[10] Takayama *et al.* reported five cases with MacTel 1, treated with 2 to 3 intravitreal bevacizumab over one year, among which only one eye showed a reduction in macular edema and an improvement in visual acuity.[11] Finally, Moon *et al.* also reported seven patients with MacTel 1 treated with intravitreal bevacizumab during 4 months. Although a significant decrease in CMT was observed on SD-OCT, there was no significant improvement in visual acuity.[12] In idiopathic macular telangiectasia type 2 (or MacTel), several studies have demonstrated that anti-VEGF therapy by bevacizumab or ranibizumab did not improve the visual acuity on the long-term, although it reduced leakage from telangiectasia in the non-proliferative form of the disease.[29-33]

In Coats' disease, which belongs to the same spectrum of microvascular disorders as MacTel 1,[5] anti-VEGF agents have become an effective adjunct therapy in the management of retinal exudation.[34,35,36] Their clinical efficacy is supported by elevated VEGF levels in the subretinal fluid[37] and aqueous humor[38] of eyes with Coats' disease, as compared to control eyes from age-matched patients with rhegmatogenous retinal detachment or congenital cataract, respectively. Moreover, immune-localization of VEGF and VEGF-receptors were performed on enucleated eyes with advanced Coats' disease,[39] and showed that VEGF-A was expressed in vascular endothelial cells and macrophages, and that VEGF-R2 (mediating angiogenesis after VEGFA stimulation) was localized in endothelial cells lining abnormal vessels, but not VEGF-R1/Flt1 (mediating vascular permeabilization and cell migration, and possibly modulating VEGF-R2 activation[16]) nor VEGF-R3 (signaling lymphangiogenesis). In contrast to MacTel 1, these data indicate that the VEGF-A-mediated VEGF-R2 pathway is specifically activated in Coats' disease, supporting the better response to bevacizumab or ranibizumab in Coats' disease than in MacTel 1. Similarly, PlGF was not detected in 18 aqueous humors from patients with wet age-related macular degeneration (AMD),[40] supporting the efficacy of bevacizumab in wet AMD.

In contrast, the higher efficacy of aflibercept over specific anti-VEGF antibodies in patients with MacTel 1, previously reported[14,15] and observed in our case series, suggest that the PlGF-mediated VEGF-R1/Flt1-pathway is involved in the

pathophysiology of MacTel 1, leading to vascular abnormalities such as telangiectasias, microaneurysms and vascular tortuosity. This assumption is supported by the increased aqueous humor levels of PlGF in MacTel 1 eyes as compared to age-matched healthy controls.

In the healthy retina, the level of PlGF expression in endothelial cells is 100-fold higher than the expression of VEGF,[41] and VEGF-R1/Flt-1 is the major VEGF receptor expressed in endothelial cells and in pericytes.[42] In our previous experimental study, long-lasting over-expression of rat PlGF in the rat eye induced vascular tortuosity and aneurysmal dilation of retinal capillaries, without neovascularization.[24] Similarly, overactivation of the PlGF-VEGFR-1/Flt-1 pathway induced a substantial increase in the branching, tortuosity, and leakiness of vessels in different organs of rodent models including skin,[43] and branches of the aorta.[44] Moreover, in MacTel 1 patients, macular edema results from vascular abnormalization and leakage without true neovascularization,[3] which is consistent with the non-elevated VEGF-A levels measured in their aqueous humor. Along with the telangiectasia, variably extended, focal areas of decreased perfusion are a classical finding in MacTel 1.[2,3] This observation was recently confirmed using OCTA.[45] Under these minimally ischemic conditions, PlGF could be a major player in the development of abnormal vessels, as shown here by the positive correlation between aqueous PlGF levels and the extension of capillary loss in the superficial and deep capillary plexus on optical coherence tomography angiography. In addition, higher levels of the soluble VEGFR-1 (sFlt-1), which binds with a high affinity to both PlGF and VEGF-A,[46] were measured in MacTel 1 eyes, as compared to control eyes, indicating a possible counter-regulatory increase in sFlt-1 in response to high PlGF levels. Levels of the soluble form of the angiopoietin receptor Tie-2 were also higher in MacTel 1 eyes. Interestingly, the Flt-1/VEGF signaling,[47] and the Ang-Tie2 signaling are involved in the loss of pericytes,[48] which could contribute to microaneurysm formation.[42]

The role of VEGF-A has also been questioned in other aneurysmal disorders affecting smaller or larger vessels. For instance, in abdominal aortic aneurysm, no significant difference in VEGF-A expression was demonstrated between the aortic wall of pathologic specimens and normal aortas from organ donors, but the expression of VEGF-C and VEGF-D was significantly increased in the abluminal layer of the aorta.[49] Moreover, the difference in angiogenic factor levels could affect the response to treatments, as in colo-rectal cancer where high circulating levels of VEGF-D are suspected to reduce the efficacy of bevacizumab therapy.[50] Remarkably, VEGF-D, but not VEGF-A levels, were significantly increased in the aqueous humor of MacTel 1 patients, suggesting it may also contribute to abnormal retinal vessel dilation and to resistance to intravitreal bevacizumab.

A similar approach has been recently proposed by Noma and collaborators, who investigated the aqueous profile of angiogenic factors in retinal vein occlusions[51,52] and found increased levels of VEGF-A, PlGF, and sFlt-1 compared to control eyes. Noticeably, microvascular remodeling causing secondary telangiectasia occur in retinal vein occlusions that may be PlGF-mediated. In contrast to MacTel 1, macular edema caused by vein occlusions respond favorably to bevacizumab,[53,54] ranibizumab[55,56] or aflibercept[57] therapy, which may be linked to the relative elevation of both VEGF-A and PlGF in the ocular media of these patients.

The present study has several limitations, including the small sample size, due to the low prevalence of MacTel 1. The only way to increase the statistical power and significance would be to get more samples from Mactel 1 patients, which requires an

inordinate amount of time and would hinder reporting of a worthwhile treatment. In addition, the follow-up duration was limited to 12 months, due to the recent availability of aflibercept, and we did not report the follow-up on OCTA for possible microvascular changes with aflibercept therapy, also due to the recent availability of this imaging technology. Also, other angiogenic or inflammatory factors could have been assessed with the multi-array immunoassay experiment, but we focused on the major angiogenic factors and receptors of the VEGF family presumed to be involved in retinal vascular diseases.

In conclusion, we found that MacTel 1 patients with macular edema have higher aqueous humor levels of PlGF, but not VEGF-A, as compared to sex and age-matched controls. Aflibercept, a neutralizer of both VEGF-A and PlGF, exerts beneficial anatomical and functional effects in these patients who did not show a good response to other therapy than aflibercept. To elucidate this effect and the observed angiogenic profile a hypothesis suggesting PlGF-VEGFR-1(Flt-1) pathway activation in Mactel 1 was generated, that best explained the data. These results should be confirmed by larger prospective studies.

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TABLES AND FIGURES

Treatments Received Before Aflibercept						
Eye #	Age, years	Sex	Laser photocoagulation	Intravitreal injections (Number)	Central macular thickness before aflibercept initiation, µm	Intravitreal aflibercept injections over 12 months
1	71	M	Macular + Extramacular	Ranibizumab (8)	528	8
2	68	M	Macular + Extramacular	Ranibizumab (1)	394	7
3	56	M	Macular + Extramacular	Bevacizumab (10)	348	5
4	45	M	Macular	Bevacizumab (6)	396	5
5	54	M	Macular (subthreshold) + Extramacular	None	595	7
6	74	M	Macular + Extramacular	Bevacizumab (6)	393	8
7	72	F	Macular + Photodynamic therapy	Bevacizumab (2) + Ranibizumab (2) + Dexamethasone (1)	508	8
8	64	M	Macular	Bevacizumab (5)	312	5

Table 1. Clinical characteristics and treatment history of eight patients with macular telangiectasia type1, refractory to previous therapies and treated by intravitreal aflibercept during a 12-month period.

Mean ± SD	Baseline	12 months	*P*-value[a]
Best-corrected visual acuity, ETDRS letter score (Snellen)	79.6 ± 16.3 (~20/52)	88.0 ± 11.2 (~20/35)	.042
Central macular thickness, µm	434.3 ± 98.0	292.5 ± 58.6	.014

Table 2. Functional and anatomical outcome of intravitreal aflibercept in eight patients with macular telangiectasia type 1. Baseline values were recorded one month after the last administration of the previous intravitreal or laser treatment. ETDRS, Early Treatment Diabetic Retinopathy Study; SD, Standard Deviation; SD-OCT, spectral-domain Optical Coherence Tomography
[a] Wilcoxon signed rank test

Concentrations Mean ± SD	Controls (pg/mL)	MacTel 1 (pg/mL)	Fold change MacTel 1 *vs* Controls	*P* value[a]
sFlt1	173.9 ± 71.17	755.9 ± 1050	× 4.3	.013
PlGF	2.1 ± 1.06	4.5 ± 2.62	× 2.2	.029
Tie-2	5.0 ± 3.73	18.7 ± 9.02	× 3.7	.019
VEGF-A	140.9 ± 44.01	187.3 ± 209.7	× 1.3	.950
VEGF-C	5.3 ± 5.63	13.2 ± 6.55	× 2.4	.110
VEGF-D	0.4 ± 0.40	6.8 ± 7.14	× 17.4	.049
bFGF	0.9 ± 0.65	3.9 ± 4.16	× 4.3	.060

Table 3. Angiogenic factors levels in aqueous humors of healthy control subjects and patients with macular telangiectasia type 1, determined on a multi-array immunoassay. bFGF, basic Fibroblast Growth Factor; ETDRS, Early Treatment Diabetic Retinopathy Study; MacTel 1, Macular telangiectasia type 1; PlGF, Placental Growth Factor; SD, Standard Deviation; sFlt1, soluble VEGF receptor 1; Tie-2, Tyrosine kinase with immunoglobulin-2 and EGF-like domains; VEGF, Vascular Endothelial Growth Factor

[a] Mann-Whitney test

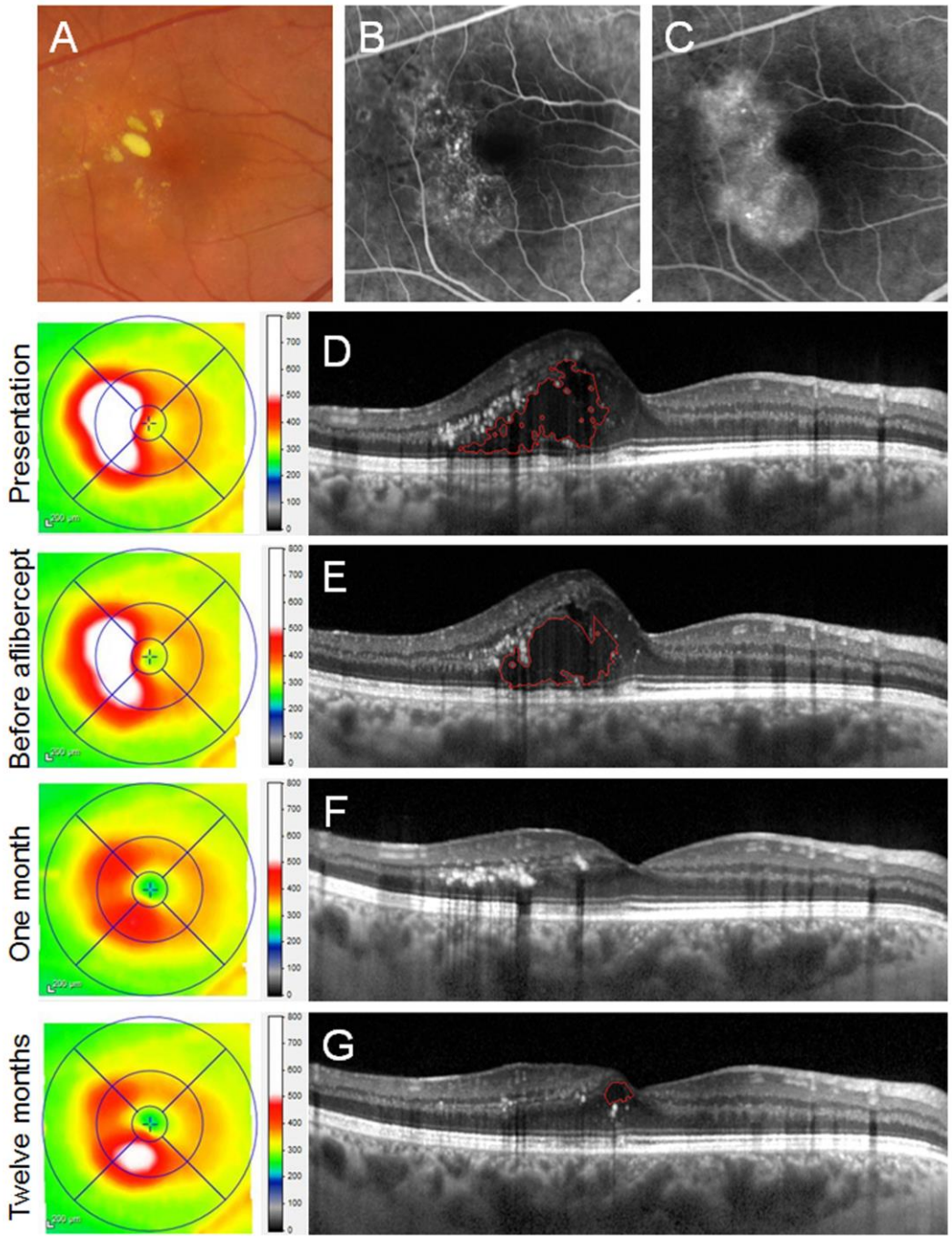


Figure 1. Differential effects of bevacizumab and aflibercept on macular edema in a 45-year-old patient with macular telangiectasia type 1 (Case 4). **(A)** Color fundus photograph showing capillary dilations and hard exudates. **(B-C)** Fluorescein angiography frames at 47 seconds **(B)** and 3.5 minutes **(C)** after dye injection showing leaky microaneurysms. **(D-G)** Horizontal optical coherence tomography B-scans of the macula acquired at different time points: at initial presentation **(D)**, one month after the last of six intravitreal bevacizumab injections administered over 7 months **(E)**, one **(F)** and twelve **(G)** months after the first intravitreal aflibercept injection. The patient received five intravitreal aflibercept injections over the 12-month follow-up. On each optical coherence tomography image, intraretinal cystoid cavities were outlined by a red line using a semi-automated algorithm.

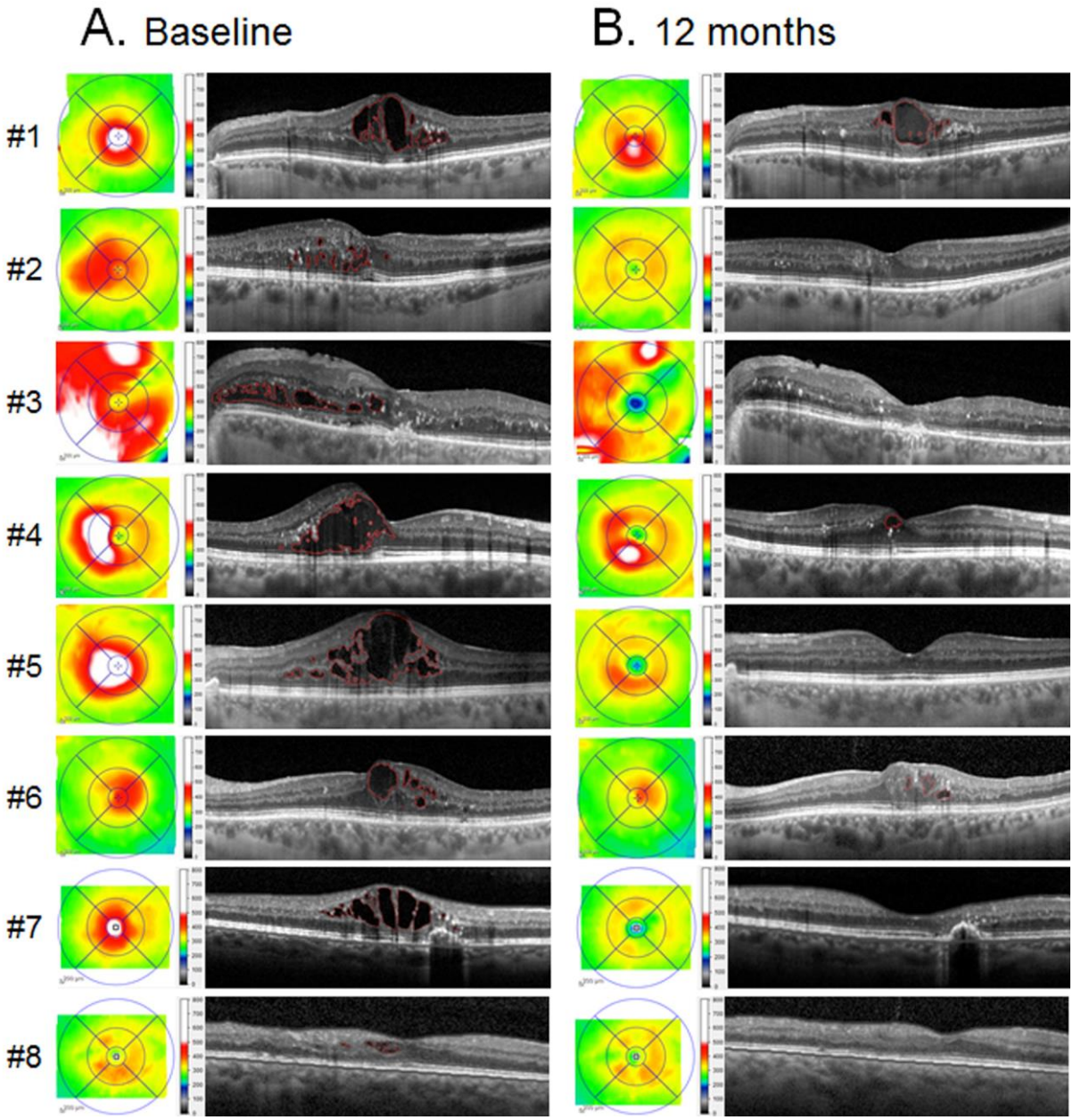


Figure 2. Clinical effect of aflibercept intravitreal therapy over 12 months in eight patients with macular telangiectasia type 1. (A) Optical coherence tomography thickness maps and horizontal b-scans through the fovea at baseline and **(B)** 12 months after initiation of intravitreal aflibercept. Central macular thickness and the area of cystoid spaces on the horizontal b-scans improved in all patients. The regions identified by a semi-automated algorithm as cystoid spaces were outlined by a red contour.

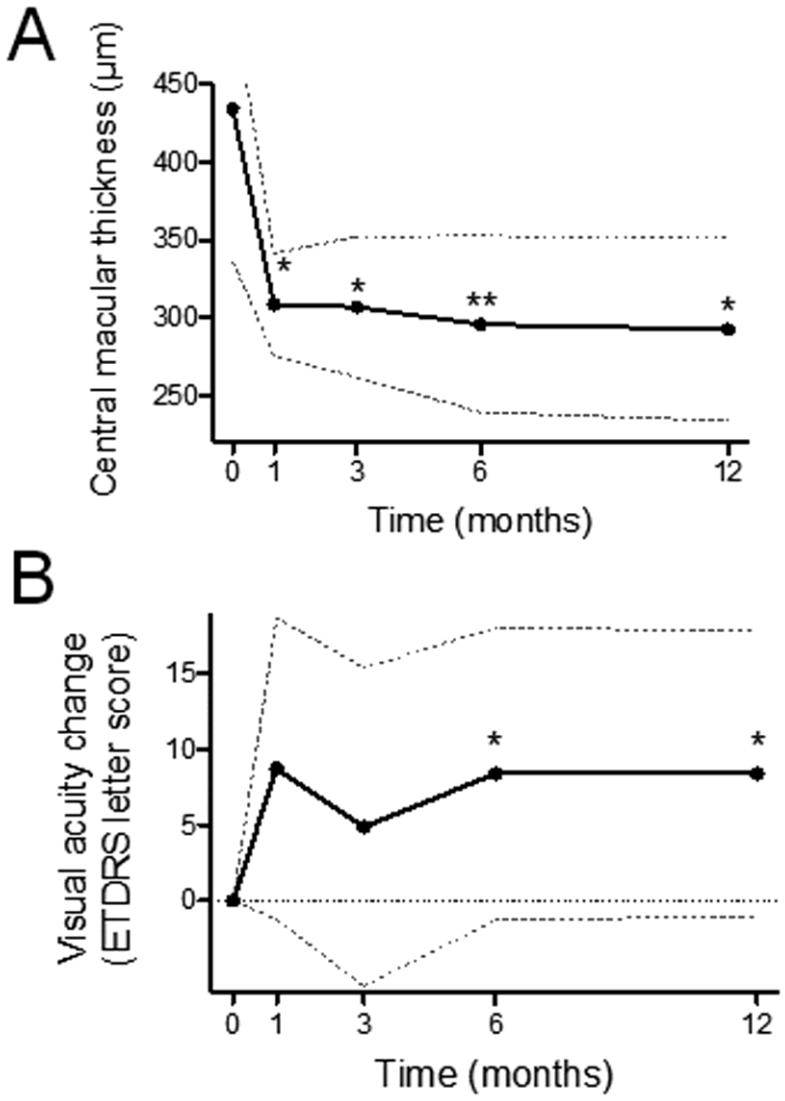


Figure 3. Anatomical and visual effect of intravitreal aflibercept therapy in eight patients with macular telangiectasia type 1, over twelve months.
(A) Mean central macular thickness. **(B)** Best-corrected visual acuity change (ETDRS letter score). All parameters were assessed at baseline, 1, 3, 6 and 12 months. The inferior and superior dotted lines indicate the standard deviation. Mean values were compared to baseline using a Wilcoxon paired test (*P<0.05; **P<0.01).

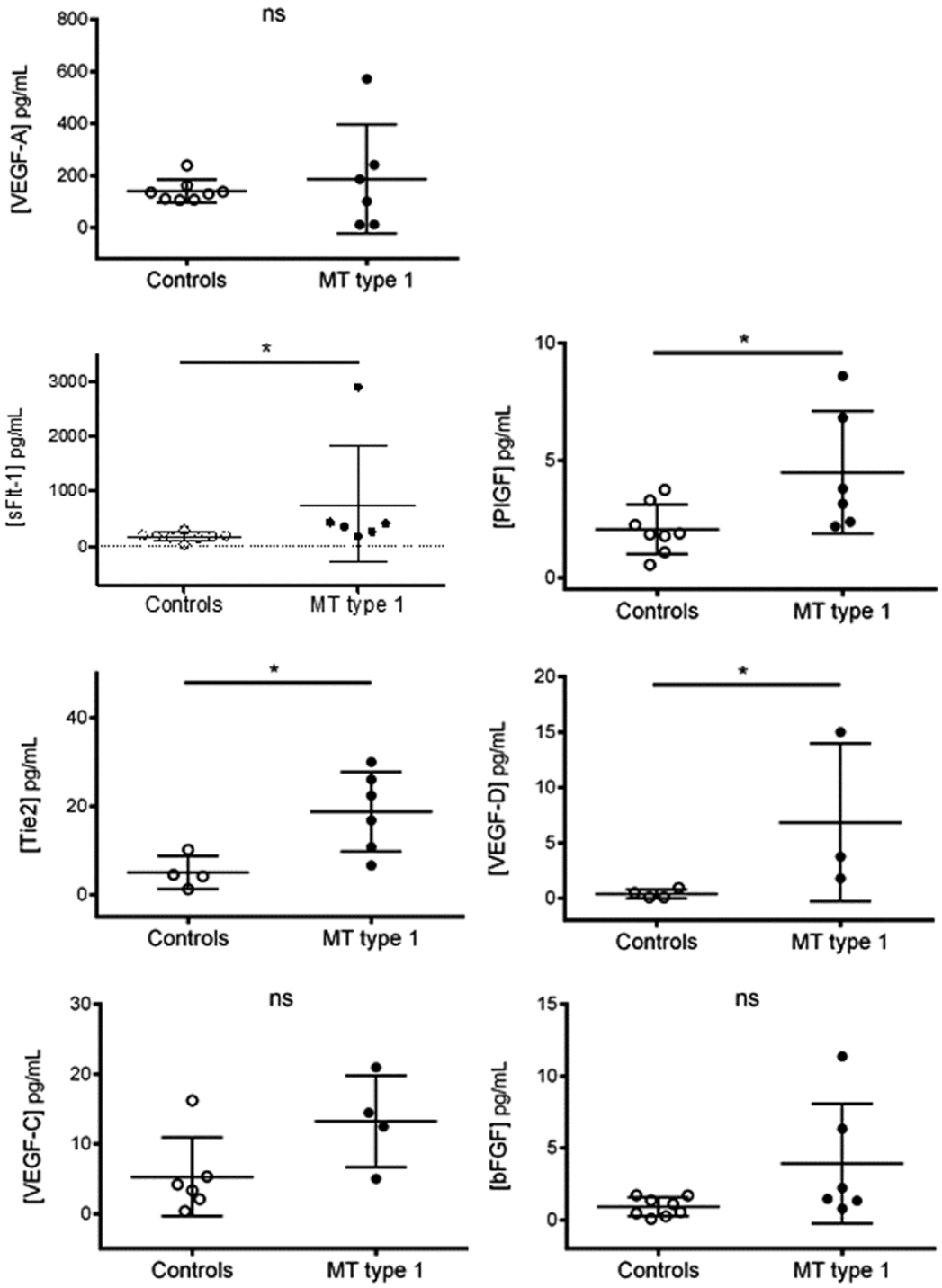


Figure 4. Angiogenic factors profile in the aqueous humor determined by a multi-array high-sensitive immunoassay. VEGF-A, sFlt-1, PlGF, Tie-2, VEGF-D, VEGF-C and bFGF levels of male patients with macular telangiectasia type-1 (n=6, black dots) were compared to those of healthy age-matched male controls undergoing cataract extraction (n=8, white dots). The levels of Tie-2, VEGF-C and VEGF-D were below the detection threshold in some aqueous humor samples, explaining the lower number of represented values. Concentrations were compared between affected and control subjects using a Mann-Whitney U test. **P* <.05; ***P* <.01; ns, not significant.

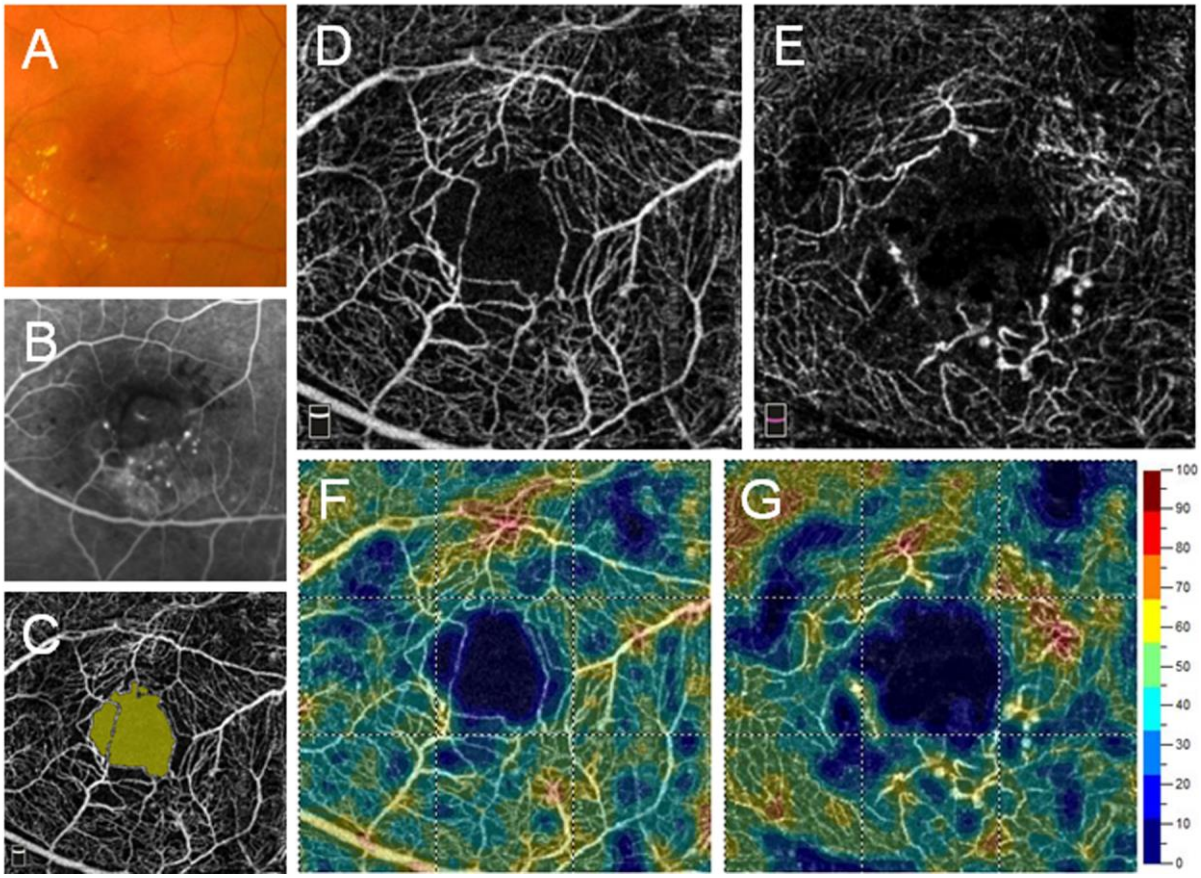
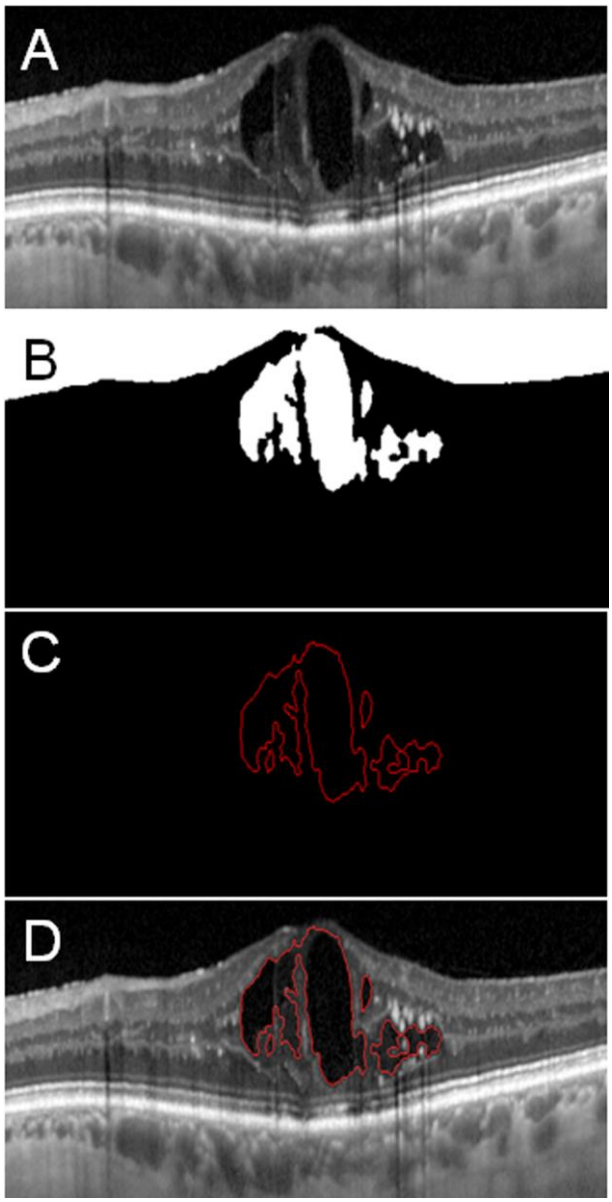


Figure 5. Multimodal imaging in a 71-year-old male patient with macular telangiectasia type 1 affecting his left eye (Case 1)**. (A)** Color fundus photograph showing telangiectasic microaneurysms and hard exudates. **(B)** Early-frame fluorescein angiogram (1 minute after dye injection) and **(C)** identification of the foveal avascular zone area on a 3×3-mm optical coherence tomography angiography image. **(D)** 3×3-mm optical coherence tomography angiography images of the superficial and **(E)** deep capillary plexus used to assess the corresponding capillary densities **(F-G)**. The deep plexus shows pronounced capillary telangiectasis and microaneurysm formation in the inferotemporal macula.

SUPPLEMENTAL DATA



Supplemental Figure. Semi-automated method to detect intraretinal cysts on optical coherence tomography. **(A)** Original horizontal B-scan spectral-domain optical coherence tomography through the fovea. **(B)** Detection of hyporeflective spaces by binary transformation. **(C)** Identification of boundaries of hyporeflective spaces, outlined in red. **(D)** Final image with cyst boundaries outlined in red, superimposed over the original B-scan.

	Angiogenic factors levels in aqueous humor (pg/mL)							SD-OCT	OCT angiography			
Eye	sFlt-1	PlGF	Tie-2	VEGF-A	VEGF-C	VEGF-D	bFGF	Baseline central macular thickness, µm	Perifoveal density of superficial capillary plexus	Perifoveal density of deep capillary plexus	Foveal avascular zone area, mm^2	Baseline BCVA, ETDRS letter score (Snellen VA)
1	418.05	3.79	22.41	12.16	5.03	U.D.	1.34	528	45.12	42.32	0.557	68 (~20/87)
2	432.49	6.83	16.78	571.91	U.D.	3.74	11.37	394	43.4	45.94	0.42	95 (~20/25)
3	353.38	8.60	25.98	100.86	20.95	1.79	2.23	348	38.61	39.04	1.098	48 (~20/220)
4	179.16	2.19	10.75	241.11	14.46	U.D.	0.79	396	52.83	57.97	0.199	99 (~20/21)
5	2890.88	2.39	29.94	11.47	12.49	15.01	6.33	595	50.6	48.49	0.603	83 (~20/44)
6	261.27	3.16	6.60	186.33	U.D.	U.D.	1.46	393	50.93	52.42	0.205	84 (~20/42)

Supplemental Table1.docx

Case-by-case values of angiogenic factor levels in aqueous humor, spectral-domain optical coherence tomography and optical coherence tomography angiography parameters, and visual acuity levels in six patients with macular telangiectasia type 1 who underwent aqueous humor tap. BCVA, Best-Corrected Visual Acuity; bFGF, basic Fibroblast Growth Factor; OCT, Optical Coherence Tomography; PlGF, Placental Growth Factor; SD-OCT, Spectral Domain OCT; sFlt1, soluble VEGF receptor 1; Tie-2, Tyrosine kinase with immunoglobulin-2 and EGF-like domains; U.D., Undetectable; VEGF, Vascular Endothelial Growth Factor

P-values (*r*) [a]	SD-OCT	OCT angiography		
	Baseline central macular thickness, µm	Perifoveal density of superficial capillary plexus	Perifoveal density of deep capillary plexus	Foveal avascular zone area, mm^2
sFlt-1, pg/mL	0.4	0.4	0.4	0.2
PlGF, pg/mL	0.2	0.03 (*r* = -0.89)	0.03 (*r* = -0.89)	0.2
Tie-2, pg/mL	0.5	0.2	0.2	0.03 (*r* = 0.89)
VEGF-A, pg/mL	0.4	0.6	0.6	0.2
VEGF-C, pg/mL	0.3	0.9	0.9	0.8
VEGF-D, pg/mL	0.3	0.3	0.3	1.0
bFGF, pg/mL	0.9	0.5	0.5	0.4

Supplemental Table2. Correlation between anatomical and biological parameters in six patients with macular telangiectasia type 1. bFGF= basic Fibroblast Growth Factor; OCT, Optical Coherence Tomography; PlGF, Placental Growth Factor; SD-OCT, Spectral Domain OCT; sFlt1= soluble VEGF receptor 1; Tie-2= Tyrosine kinase with immunoglobulin-2 and EGF-like domains; VEGF, Vascular Endothelial Growth Factor