

ARTICLE



Type one macular neovascularization in central serous chorioretinopathy: Short-term response to anti-vascular endothelial growth factor therapy

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PURPOSE: The aim of this study was to assess the short-term effect of anti-vascular endothelial growth factor (VEGF) treatment on type 1 macular neovascularization (MNV) secondary to central serous chorioretinopathy (CSCR) and to identify potential predictive factors for treatment response using multimodal imaging.

METHODS: Retrospective, multicentre study in CSCR patients with MNV detected by OCT-angiography and treated with anti-VEGF injections. Clinical and multimodal imaging data before and after anti-VEGF injections was reviewed. Univariate and multivariate linear regression analyses were performed to evaluate associations between the change in central macular thickness (CMT) after anti-VEGF therapy and other factors.

RESULTS: Forty patients were included. One month after receiving a mean number of 2.7 anti-VEGF intravitreal injections, visual acuity increased significantly from 0.46 ± 0.3 logMAR at baseline to 0.38 ± 0.4 logMAR ($p = 0.04$). The CMT and foveal serous retinal detachment (SRD) decreased significantly from 330 ± 81.9 μm at baseline to 261.7 ± 63.1 μm after treatment ($p < 0.001$) and from 145.1 ± 98.8 μm at baseline to 52.6 ± 71.3 μm ($p < 0.001$), respectively. Subretinal fluid and/or intraretinal fluid were still present in 18 eyes (45%) one month after treatment. In the multivariate analysis, a higher SRD height was associated with a greater CMT change ($p = 0.002$) and a lower CMT change with the presence of subretinal hyperreflective material (SHRM) ($p = 0.04$).

CONCLUSION: Fluid resorption was incomplete in about half of the patients with MNV secondary to CSCR after anti-VEGF injections. Shallower SRD or the presence of SHRM were predictors of poor response to anti-VEGF.

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INTRODUCTION

Central serous chorioretinopathy (CSCR) is characterized by the presence of subretinal fluid (SRF) associated with pigment epithelium detachment and choroidal venous dilations. Several clinical forms of CSCR have been described. The acute forms usually resolve within 4–6 months and generally have a good visual prognosis. The chronic forms (also called diffuse retinal epitheliopathy) are associated with extended retinal pigment epithelium (RPE) damage and, in some cases, with flat irregular pigment epithelium detachments (FIPED) and type-1 macular neovascularization (MNV) [1]. The exact pathogenesis of CSCR remains unclear but multimodal imaging findings indicate that choroidal and RPE changes might precede episodes of SRF and subsequent retinal and RPE damage [2, 3] integrating CSCR in the large spectrum of pachychoroid-associated diseases [4]. Recently, Siedlecki et al have proposed a new classification of pachychoroid spectrum diseases considering that Type 1 MNV associated with CSCR should be referred to as “pachychoroid neovasculopathy” [5].

OCT-angiography (OCT-A) has considerably improved the detection of MNV in eyes with FIPED as compared with spectral domain-OCT, fluorescein angiography (FA), and indocyanine green angiography (ICGA) [6, 7] but has also raised new therapeutic challenges. Indeed, it is almost impossible to distinguish the origin of the subretinal fluid in cases of CSCR associated with MNV and to assert that it results from the neovascular activity and not from the underlying pathology. Whilst the efficacy of intravitreal injections (IVIs) of anti-VEGF in MNV due to age-related macular degeneration (AMD) [8, 9] or myopia [10] is well established by several randomized clinical trials, the efficacy of anti-VEGF for MNV associated with CSCR remains poorly documented. Previous retrospective studies including a limited number of subjects have reported a moderate clinical response to anti-VEGF [11–13]. The prospective Minerva study [14] has reported the efficacy of IVIs of ranibizumab in treating MNV of various aetiologies, including CSCR. Other therapeutic options include anti-VEGF therapy combined with half-dose (fluence) photodynamic therapy [15].

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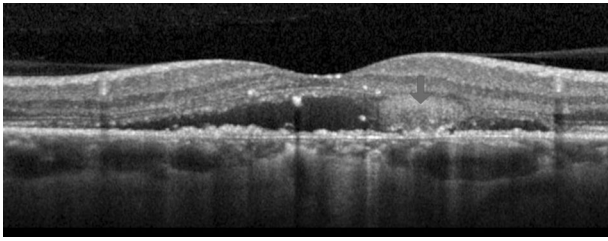


Fig. 1 OCT scan from an active CSCR patient. SD-OCT scan showing a subretinal hyperreflective material (SHRM) inside the subretinal detachment defined by the presence of hyperreflective material between the detached neurosensory retina and the underlying retinal pigment epithelium (arrow).

The aim of this study was to evaluate the effect of anti-VEGF injections on MNV associated with CSCR and to identify potential predictive factors for treatment response.

METHODS

Study design

This was a retrospective multicentre study conducted in the Departments of Ophthalmology of Cochin, Lariboisière, XVXX, CIL (Paris, France), and Jules Gonin Eye (Lausanne, Switzerland) hospitals between 2013 and 2018. Data of all consecutive patients with CSCR associated with type-1 MNV treated with anti-VEGF injections were retrospectively reviewed.

Ethics statement

The study was conducted in compliance with the tenets of the Declaration of Helsinki and was approved by our institutional review board (CEERB d'île de France, Paris, France).

Patients

All patients had a past history of CSCR, that is why we will use the term "type-1 MNV secondary to CSCR" rather than "pachychoroid neovasculopathy".

Inclusion criteria were (1) active CSCR with serous retinal detachment (SRD), (2) type-1 MNV detected by OCT-A, and (3) patients treated with anti-VEGF IVIs.

(4) patients treated with 3 monthly anti-VEGF injections or patients treated with one or two anti-VEGF IVIs with a complete resolution of exudative signs after the first or the second IVI.

Exclusion criteria were (1) the presence of any other retinal disease including macular drusen, AMD, high myopia, dome-shaped macula, and (2) a history of CSCR treatment including laser, photodynamic therapy, or mineralocorticoid receptor antagonist in the year before inclusion.

Study protocol

Patient medical records and imaging data were reviewed before and one month after anti-VEGF IVIs. The collected data included age, gender, history of corticosteroid intake, previous CSCR treatment, and the clinical form of CSCR. Chronic CSCR was defined by the presence of a persistent SRD for at least 6 months. In other cases, CSCR was classified as acute/recurrent.

Clinical and multimodal imaging findings were recorded including the best-corrected visual acuity (BCVA) converted into logMAR scale, fundus biomicroscopy and multimodal imaging including spectral-domain OCT (SD-OCT, Heidelberg Spectralis, Heidelberg, Germany), blue light fundus autofluorescence (FAF, Spectralis), and in most cases, FA, and ICGA (Spectralis). In all patients, type-1 MNV was detected by OCT-A (Optovue, Inc, Fremont, CA).

Image analysis

The following variables were collected based on the multimodal imaging analysis: central macular thickness (CMT), presence of SRF/IRF, the maximum subretinal detachment (SRD) height assessed by manually measuring the distance between the external limiting membrane and the RPE on the horizontal line passing through the fovea at the point of maximum fluid accumulation. The presence of subretinal hyperreflective material (SHRM) in the SRD was also evaluated on SD-OCT. SHRM was

defined by the presence of hyperreflective material between the detached neurosensory retina and the underlying RPE (Fig. 1).

The choroidal thickness (CT) was manually measured between the RPE and the inner surface of the sclera on enhanced depth imaging (EDI) horizontal B-scans as previously described [16].

Other variables were recorded: the presence/absence of gravitational tracks on fundus autofluorescence (FAF), CSCR leakage on FA, mid-phase hyperfluorescent areas consistent with a "choroidal hyperpermeability" and late-phase hyperfluorescent MNV on ICGA.

Anti-VEGF treatment

All patients received monthly IVIs of anti-VEGF corresponding either to 0.5 mg of ranibizumab (Lucentis; Novartis Pharma, AG, Basel, Switzerland) or to 2 mg of aflibercept (Eylea, Bayer, HealthCare Pharmaceuticals, Berlin, Germany). The choice of the anti-VEGF was based on the clinician's preference.

Statistical analyses

Descriptive data are presented as the mean \pm standard deviation (SD) for quantitative variables and as counts and percentages for categorical variables. Comparisons between variables were performed using a paired Wilcoxon or Mc Menar test when appropriate.

Univariate and multivariate linear regression analyses were performed to evaluate associations between the CMT change after anti-VEGF IVIs and other factors. Factors showing associations in the univariate analysis with $p < 0.1$ were included in the multivariate regression model. All p values were 2-sided and p values ≤ 0.05 were considered statistically significant.

RESULTS

Patient characteristics

Forty eyes of 40 patients met the inclusion criteria. Patients' demographics, clinical and imaging data are summarized in Table 1. Patient mean (\pm SD) age was 60.1 (\pm 9.6) years (range: 32.3–78.7). Twenty-eight patients (70%) were male. A previous corticosteroid intake was reported in 13 patients (38.2%).

Twenty-four eyes (60%) had a history of prior treatment received more than one year before inclusion (Table 1).

Most patients (90%) had chronic CSCR while 2 patients had a recurrent form and 2 patients had a history of acute CSCR. The mean (\pm SD) BCVA was 0.46 ± 0.3 LogMAR. On SD-OCT, an SRD was detected in all eyes. An IRF was associated with the SRD in 11 eyes (27.5%). SHRM inside the SRD was detected in 14 eyes (35%). The mean subfoveal CT was 393.8 ± 126.3 μ m. Gravitational tracks were detected in 16 eyes (40%). Hyperfluorescent MNV was detected in 17 eyes (48.6%) during the late phase of ICGA.

Anti-VEGF treatment

Twenty-two patients (55%) received aflibercept, and 18 patients (45%) received ranibizumab. Thirty-two patients (80%) received 3 IVIs while 5 patients (12.5%) received 2 IVIs and 3 patients (7.5%) received 1 IVI (Table 1). Indeed, in these 5 patients, a complete resolution of the SRD and/or IRF was observed on OCT one month after the last IVI.

Treatment effect at 3 months

Patients were assessed one month after receiving a mean number of 2.7 IVIs of anti-VEGF. The visual acuity and OCT findings before and after anti-VEGF therapy are summarized in Table 2. The BCVA increased significantly from 0.46 ± 0.3 logMAR at baseline to 0.38 ± 0.4 logMAR after treatment ($p = 0.04$). The CMT decreased significantly from 330 ± 81.9 μ m at baseline to 261.7 ± 63.1 μ m after treatment ($p < 0.001$). The SRD height decreased significantly from 145.1 ± 98.8 μ m at baseline to 52.6 ± 71.3 μ m after treatment ($p < 0.001$). The CT measurement was available for 33 eyes. The subfoveal CT slightly decreased from 367.3 ± 101.7 μ m at baseline to 351.2 ± 99 μ m after treatment ($p = 0.003$). SRF and/or IRF were detected in 18 eyes (45%) one month after 3 IVIs of anti-VEGF. Thus, treatment was effective in drying completely the retina in 22

Table 1. Clinical and Imaging Data of patients with central serous chorioretinopathy (CSCR) associated with choroidal neovascularization (CNV) before intravitreal injections of anti-VEGF.

Characteristics	
Demographics	
Age, mean \pm SD, years (range)	60.1 \pm 9.6 (32.3–78.7)
Gender, males (%)	28 (70%)
Corticosteroid intake, <i>n</i> (%) (missing = 6)	13 (38.2%)
Previous CSCR treatments	
Laser Photocoagulation, <i>n</i> eyes (%)	11 (27.5%)
PDT, <i>n</i> eyes (%)	10 (25%)
Eplerenone/Spirolonactone, <i>n</i> patients (%)	7 (17.5%)
Clinical form of CSCR	
Acute/recurrent CSCR, <i>n</i> (%)	4 (10%)
Chronic CSCR	36 (90%)
BCVA (LogMAR) mean \pm SD	0.46 \pm 0.3
OCT	
Subfoveal choroidal thickness, mean \pm SD (μ m)	393.8 \pm 126.3
Central macular thickness, mean \pm SD (μ m)	330 \pm 81.9
Serous Retinal Detachment height, mean \pm SD (μ m)	153.4 \pm 89.6
Intraretinal fluid, <i>n</i> (%)	11 (27.5%)
SHRM in the subretinal detachment, <i>n</i> (%)	14 (35%)
Autofluorescence	
Gravitational tracks, <i>n</i> (%)	16 (40%)
Fluorescein Angiography	
CSCR ink-blot leakage, <i>n</i> (%) (missing = 6)	5 (14.7%)
Indocyanine Green Angiography	
Mid-phase hyperfluorescent plaques, <i>n</i> (%) (missing = 6)	18 (52.9%)
Late hyperfluorescent CNV, <i>n</i> (%) (missing = 5)	17 (48.6%)
Treatment regimen	
Aflibercept, <i>n</i> (%)	22 (55%)
Ranibizumab, <i>n</i> (%)	18 (45%)
Number of intravitreal injections, mean \pm SD	
3 intravitreal injections, <i>n</i> (%)	32 (80%)
2 intravitreal injections, <i>n</i> (%)	5 (12.5%)
1 intravitreal injection, <i>n</i> (%)	3 (7.5%)

SD Standard Deviation, PDT Photodynamic Therapy, BCVA Best-Corrected Visual Acuity, OCT Optical Coherence Tomography, CSCR Central Serous Chorioretinopathy, CNV Choroidal Neovascularization

eyes (55%). On the other hand, SRD was stable or increased in 11 eyes (27.5%) after anti-VEGF therapy.

No difference was found depending on the treatment regimen. Indeed, among patients with persistent SRD after anti-VEGF therapy, 8 patients (44.4%) received ranibizumab and 10 patients (55.6%) received aflibercept ($p = 0.95$).

Factors associated with a CMT change 3 months after anti-VEGF treatment

In the univariate analysis, a greater CMT change after anti-VEGF IVIs was associated with the female gender, a higher CMT, and a higher SRD height at baseline ($p = 0.048$, < 0.001 and < 0.001 , respectively, Table 3). The presence of SHRM in the SRD was associated with a lower CMT change ($p = 0.013$). In the multivariate analysis, a higher SRD height was associated with a greater CMT change ($p = 0.002$) and the presence of SHRM was associated with a lower CMT change ($p = 0.04$, Table 3 and Fig. 2).

Follow-up at 6 months

After 3 monthly anti-VEGF IVIs, 18 patients had persistent SRF and/or IRF (Table 2). At 6 months, the data was available for 13 out of the 18 patients. After a mean number of 5.1 anti-VEGF IVIs, the mean BCVA increased significantly from 0.67 \pm 0.3 logMAR at baseline to 0.55 \pm 0.4 logMAR after treatment ($p = 0.035$). The mean CMT decreased without reaching statistical significance from 339.6 \pm 83.8 μ m at baseline to 290.5 \pm 110 μ m after treatment ($p = 0.1$). Eleven eyes had persistent SRF after 3 anti-VEGF IVIs, and a complete resolution of the SRF was achieved in 2 (18.2%) of these eyes at 6 months. Two eyes had persistent IRF without SRF at 3 months, and a resolution of the IRF was achieved in 1 of these eyes at 6 months. Overall, 10 out of the 13 eyes (77%) still had persistent SRF/IRF after a mean number of 5.1 anti-VEGF IVIs at 6 months and 5 of them (50%) had SHRM at baseline.

DISCUSSION

Type-1 MNV is a known complication of CSCR, and is mainly observed in the chronic forms of the disease [17]. The detection of CSCR has been improved with the use of OCT-A [6, 7]. Indeed, on ICGA, a hyperfluorescent area can be secondary to the choroidal hyperpermeability in CSCR or to focal leaks and has been observed in half of CSCR patients without CNV in a previous study [6].

In our study, all MNV was confirmed using OCT-A. Whether SRF and/or IRF associated with type-1 MNV respond differently to anti-VEGF injections in CSCR compared with AMD remains controversial. While several studies have shown that MNV secondary to CSCR was associated with poorer visual outcomes compared with other forms of CSCR [17, 18], Chen et al. have recently found no significant loss of BCVA in CSCR complicated by MNV during a 3-year follow-up without any treatment [19]. But, in this cohort,

Table 2. Visual acuity and optical coherence tomography data at baseline and 1 month after intravitreal injections of anti-VEGF in patients with central serous chorioretinopathy associated with Type-1 macular neovascularization.

	Baseline	After anti-VEGF therapy	P-value
BCVA (LogMAR) mean \pm SD	0.46 \pm 0.3	0.38 \pm 0.4	0.04^a
Central macular thickness (μ m), mean \pm SD	330 \pm 81.9	261.7 \pm 63.1	<0.001^a
Subretinal detachment height (μ m), mean \pm SD	145.1 \pm 98.8	52.6 \pm 71.3	<0.001^a
Subfoveal choroidal thickness (μ m), mean \pm SD	367.3 \pm 101.7	351.2 \pm 99	0.003^a
Subretinal detachment \pm intraretinal fluid, <i>n</i> (%)	40 (100%)	18 (45%)	<0.001^b

^aWilcoxon paired signed-rank test

^bMc Nemar test

BCVA Best-Corrected Visual Acuity, VEGF Vascular-Endothelial Growth Factor, SD Standard Deviation

Statistically significant $p < 0.05$ values are in bold.

Table 3. Linear regression analyzes of factors associated with a decreased central macular thickness after anti-VEGF therapy in patients with central serous chorioretinopathy associated with Type-1 macular neovascularization.

Variables	Univariate analysis		Multivariate analysis	
	Standardized Coefficient β	P-value	Standardized Coefficient β	P-value
Age	0.275	0.086	0.160	0.154
Gender (females vs males)	0.315	0.048	0.027	0.808
Corticosteroid intake	0.142	0.423		
Previous CSCR treatments				
Laser photocoagulation	-0.102	0.533		
PDT	0.055	0.737		
Eplerenone/Spirolactone	0.104	0.523		
Clinical form of CSCR				
Acute/recurrent vs chronic CSCR	0.054	0.741		
BCVA	0.027	0.879		
OCT				
Subfoveal choroidal thickness	-0.148	0.389		
Central macular thickness	0.635	<0.001	0.173	0.257
Serous retinal detachment height	0.762	<0.001	0.540	0.002
Intraretinal fluid	-0.155	0.340		
SHRM in the subretinal detachment	-0.391	0.013	-0.238	0.041
Autofluorescence				
Gravitational tracks	-0.035	0.26		
Fluorescein angiography				
CSCR ink-blot leakage	0.054	0.76		
Indocyanine green angiography				
Mid-phase hyperfluorescent plaques	0.257	0.14		
Late hyperfluorescent MNV	-0.288	0.16		

PDT Photodynamic Therapy, CSCR Central Serous Chorioretinopathy, BCVA Best-Corrected Visual Acuity, OCT Optical Coherence Tomography, SHRM Subretinal Hyperreflective Material, MNV Macular Neovascularization
Statistically significant $p < 0.05$ values are in bold.

most of the MNV was quiescent as 25 out of the 30 eyes had no SRF. Whether SRF resulting from MNV leakage triggers more photoreceptor damage than SRF resulting from CSCR activity is unknown.

When the SRF is associated with MNV in CSCR, anti-VEGF IVIs have usually considered the first-choice therapy as in type-1 MNV-associated with AMD. Interestingly, the present study confirms previous results from Rhomdane et al. showing complete fluid resorption in 45% of 27 eyes with MNV complicating CSCR [13]. In the present study, 45% of eyes had persistent SRF or IRF one month after the induction phase of anti-VEGF IVIs and 77% of these eyes still had persistent SRF/IRF at 6 months after a mean number of 5.1 anti-VEGF IVIs. This could be explained by the difficulty to differentiate active MNV from quiescent MNV-associated with CSCR reactivation. Indeed, in a recent meta-analysis, no difference between anti-VEGF IVIs and observation has been found in acute and chronic CSCR patients [20, 21].

In these patients with persistent fluid, we could assume that the SRD was secondary to CSCR rather than to the CNV activity. Therefore, combined treatment with photodynamic therapy could be effective in these patients [22].

On the other hand, 55% of our patients experienced a complete resolution of the exudative signs after anti-VEGF IVIs. This response could be due to the efficacy of the treatment but also to the natural history of CSCR, a fluctuating disease with a spontaneous resolution of SRF. Only a randomized placebo-controlled trial could definitively confirm the efficacy of anti-VEGF IVIs in these cases.

Another objective of the study was to identify predictive factors for treatment response. These factors could help to identify patients that would benefit from anti-VEGF treatment. We found two factors associated with a response to anti-VEGF in the multivariate analysis. First, the SRD height was associated with a good response to anti-VEGF treatment. This result is consistent with the study by Romdhane et al. [13] The other predictive factor was the presence of SHRM in the SRD that correlated with a poor response to anti-VEGF treatment. The white subretinal exudate referred to as fibrin by Donald Gass has initially been described in patients treated with corticosteroids or during pregnancy [23, 24]. More recently, the presence of fibrin has been reported in up to 61% of CSCR patients based on SD-OCT [25]. Proteins are thought to enter the subretinal space through a "defect" in the RPE, the hyperreflective material of which was found located close to the leaking point [26]. The presence of SHRM/fibrin could thus be a sign of CSCR activity and could therefore explain a poor response to anti-VEGF therapy. Otherwise, in neovascular AMD, SHRM is interpreted as fibrin, but could also correspond to hemorrhage, vitelliform deposits, or shed photoreceptors [27, 28].

In AMD, as in CSCR, the SRF could originate from an alteration of the active barrier function of the RPE and the efficacy of anti-VEGF could depend on protein gradients between the vitreous, the retina, and the choroid. Indeed, it has been recently hypothesized that the effect of anti-VEGF could be mediated at least in part by VEGF-unrelated mechanisms associated with oncotic gradients [29]. In addition, in CSCR, the hyperpermeability of choroidal vessels to macromolecules such as albumin-bound to ICG suggests an increase

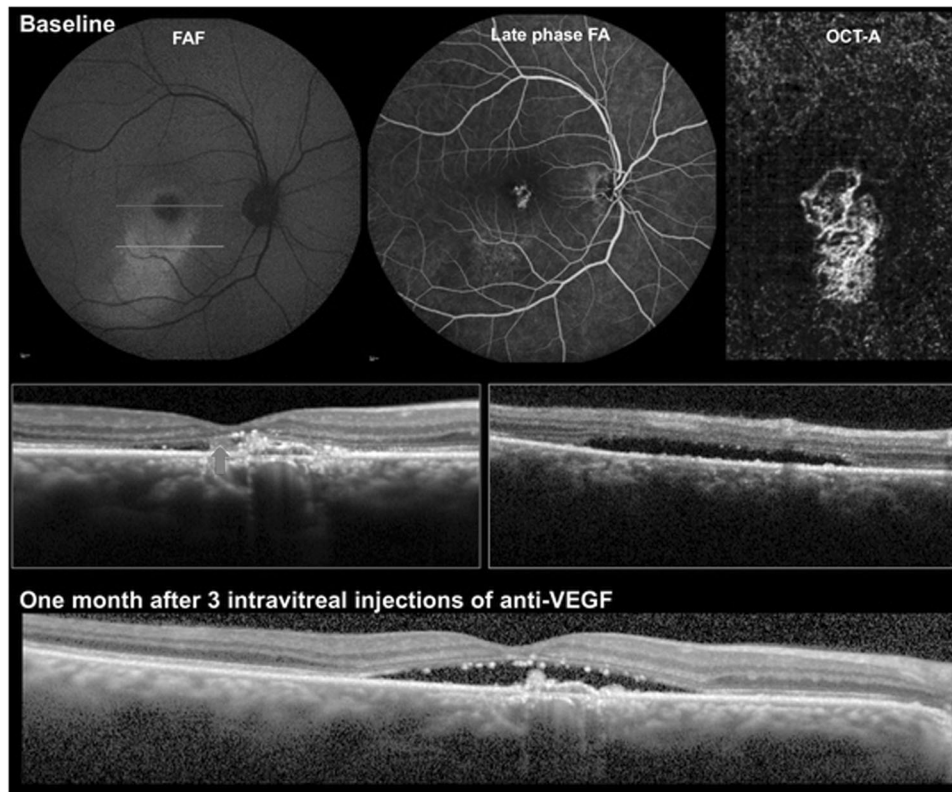


Fig. 2 A 63-year-old man with chronic central serous chorioretinopathy associated with type-1 macular neovascularization (MNV) treated with 3 intravitreal injections of ranibizumab. Top left: Fundus autofluorescence (FAF) shows a hyperautofluorescent gravitational track. Top middle: Late-phase fluorescein angiography (FA) shows a poorly defined hyperfluorescent macular area. Top right: OCT-angiography (OCT-A) shows type-1 MNV. Middle: SD-OCT B-scans, the subretinal fluid contains hyperreflective subretinal material (right middle, arrow). Bottom: After 3 injections of ranibizumab, the foveal subretinal fluid is increased.

in protein concentration in the choroid stroma. The passage of macromolecules in the SRF would further decrease the oncotic effect of anti-VEGF injected into the vitreous resulting in lower efficacy. In AMD as in CSCR, type-1 MNV does not regress under intensive anti-VEGF therapy, but a restoration of the RPE function either spontaneously in fluctuant CSCR forms or using photodynamic therapy or other treatment modalities could help to dry the retina. Whether this will be associated with a better visual outcome in the long term in CSCR-associated MNV remains to be demonstrated.

This study has some limitations, including its retrospective design, its short follow-up, and the absence of a placebo-controlled group. Indeed, the spontaneous improvement of exudative signs originating from CSCR could have led to an overestimate of the efficacy of anti-VEGF therapy. Another limitation is the lack of quantitative OCT-A analysis.

Despite these limitations, our study confirmed in an independent cohort that 45% of patients with CSCR-associated MNV show persistent exudative signs one month after 3 monthly anti-VEGF IVs. A shallower SRD or the presence of SHRM were predictors of a poor response to anti-VEGF. Further prospective controlled studies are needed to confirm these results.

SUMMARY

What was known before

- MNV in CSCR is treated with anti-VEGF. Some of the patients don't respond to treatment.

What this study adds

- We identified factors associated with good response, which could be useful for patient information.

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AUTHOR CONTRIBUTIONS

RL was responsible for designing the protocol, writing the protocol, conducting the search, extracting and analyzing data. FBC, IM, JRM, SM, RT, and AG were responsible for providing data, interpreting results, writing discussion. EB was responsible for designing the protocol, writing the protocol, conducting the search, extracting and analyzing data, and interpreting results.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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