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Clinical outcomes of a treat-and-extend regimen with intravitreal aflibercept injections in patients with choroidal neovascularization secondary to chronic central serous chorioretinopathy

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Purpose: *To evaluate 12-month clinical outcomes of a treat-and-extend regimen with intravitreal aflibercept injections in patients with occult (type 1) choroidal neovascularization (CNV) secondary to chronic central serous chorioretinopathy (CSC).*

Methods: *This was a prospective observational single-center study involving 24 patients (24 eyes) with occult (type 1) CNV secondary to chronic CSC. All patients received three initial loading doses of intravitreal 2 mg (0.05 ml) aflibercept at 4-weekly intervals, followed by a treat-and-extend protocol. The primary outcome was best-corrected visual acuity (BCVA) at 12 months. Statistical analyses were conducted and graphs were created using Statistica 10.0 software.*

Results: *Mean BCVA increased significantly from 0.44 ± 0.35 at baseline to 0.58 ± 0.3 at month 12 (p = 0.01). At month 12, complete resolution of SRF was observed in 18 eyes (75%). The mean number of intravitreal aflibercept injections over 12 months was 7.5 ± 1.4.*

Conclusion: *Treat-and-extend intravitreal aflibercept is an effective and safe approach for managing patients with occult (type 1) CNV secondary to chronic CSC.*

Introduction

Chronic central serous chorioretinopathy (CSC) is a chorioretinal disease that is characterized by multifocal damage to the retinal pigment epithelium (RPE) and photoreceptors, persistent subretinal fluid (SRF) and increased choroidal thickness. These changes may contribute to the development of type 1 (subretinal pigment epithelium) choroidal neovascularization (CNV) [1-5]. The factors associated with macular neovascularization secondary to CSC were older age, higher rates of chronic CSC and recurrence, and foveal leakage points on fluorescein angiography (FA) [6]. Submacular CNV was a factor associated with reduced visual acuity in patients with idiopathic CSC [7, 8].

The rate of CNV in chronic CSC has been reported to range from 2%-18% [1, 5, 9]. CNV may develop in 24% of chronic CSC patients with mean disease duration ≥ 17 years [10]. The rate of detection of CNV in chronic CSC patients, however, increased to 35.6 – 58% [11-13] with advent of optical coherence tomography (OCT) angiography (OCTA).

Photodynamic therapy (PDT) and anti-vascular endothelial growth factor (VEGF) therapy are current treatment options for CNV in chronic CSC. Several studies reported on the success of vertreprofin in chronic CSC patients with CNV [14-17]. Hu and colleagues [17] reported that 44.1% of eyes treated with half-dose verteporfin PDT for CSC received additional anti-VEGF, half-dose PDT treatment, or both due to persistent or recurrent SRF. Peiretti and colleagues [18] concluded that PDT and intravitreal VEGF inhibitors alone or combined showed similar clinical effects in chronic CSC eyes with CNV [18].

The MINERVA study proposed using ranibizumab as a first-line treatment in eyes with CNV associated with chronic CSC. They used a dosing strategy with two initial ranibizumab loading doses every 4 weeks, followed by an as needed (pro re nata (PRN)) regimen [19]. Subsequently, Jung and colleagues [20] compared the efficacy of intravitreal injection of ranibizumab and aflibercept

for patients with pachychoroid neovasculopathy and concluded that aflibercept was superior to ranibizumab in achieving dry macula and reducing choroidal choroidal thickness at 3 months. It is not uncommon that patients with CNV secondary to CSC treated with ranibizumab or aflibercept have poor anatomical outcome with persistent SRF. Thus, complete fluid resolution was observed in 45% of patients treated with aflibercept or ranibizumab (with a loading dose and PRN regimen) [21]. Others [22] used an extended 6-month anti-VEGF (aflibercept or ranibizumab) upload for CNV secondary to chronic CSC and observed complete SRF resolution in 52.4% of the eyes after six injections.

The purpose of this study was to evaluate 12-month clinical outcomes of a treat-and-extend regimen with intravitreal aflibercept injections in patients with occult (type 1) CNV secondary to chronic CSC.

Methods

This was a prospective observational single-center study involving 24 patients (24 eyes) with occult (type 1) CNV secondary to chronic CSC. All patients received 2 mg (0.05 ml) aflibercept. The study was conducted at the Department of Laser Microsurgery of Eye Disease, SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the NAMS of Ukraine". This study was approved by the local bioethics committee (committee meeting minutes of April 12, 2021) and informed consent was obtained from all study subjects. All procedures performed in the study were in accordance with the ethical standards of the Helsinki Declaration.

The inclusion criteria were the age ≥ 18 years and the active CNV secondary to chronic CSC. Patients were excluded if they had polypoidal choriovasculopathy, other macular diseases, a less than 3-month history of PDT or laser coagulation, history of intraocular surgery, other eye diseases affecting visual acuity (glaucoma, immature or mature cataract), acute intraocular or periocular inflammation, or treatment with corticosteroids. Patients were allowed to receive concomitant treatment with oral spironolactone or eplerenone. Patients received three initial loading doses of intravitreal 2 mg (0.05 ml) aflibercept at 4-weekly intervals, followed by a treat-and-extend protocol. The protocol included aflibercept treatment at 4-weekly intervals until SRF resolution; thereafter, the interval was extended by 2 weeks. The dosing interval was to be shortened by 2 weeks until the stabilization of functional and/or anatomical characteristics, whenever symptoms or signs of relapse (with a reduction in visual acuity and OCT evidence of intraretinal fluid or SRF) occurred [23]. However, in no case was the interval shorter than 4 weeks.

Informed consent was obtained after patients were informed on the technique, treatment medication and regimen, and the risks of complications. Intavitreal aflibercept was injected in a standard sterile fashion in the operating room [24].

Patients underwent Snellen decimal best-corrected visual acuity (BCVA) assessment, intraocular pressure (IOP) measurement, OCT, retinal FA, and OCTA. The follow-up period for each patient was 12 months. BCVA assessment, IOP measurement, OCT and OCTA (SOCT Copernicus OPTOPOL Technology S.A., Zawiercie, Poland), and FA (TRC 50 – EX; Topcon, Tokio, Japan), were performed at baseline and monthly and at any additional time point if required.

The primary outcome was BCVA at 12 months. Secondary outcomes included SRF resolution, central retinal thickness (CRT), subfoveal choroidal thickness (SFCT), number of injections per eye, interval between the last aflibercept injection and the final visit, and treatment safety at 12 months. CRT and SFCT were measured using OCT calipers at each visit.

Statistical analyses were conducted using Statistica 10.0 (StatSoft, Tulsa, OK, USA) software. Student t-test was used for intragroup comparisons. Data are presented as mean and standard deviation (SD). Graphs were created using Statistica 10 software. The level of significance $p \leq 0.05$ was assumed.

Results

Twenty-four patients (24 eyes) with occult (type 1) CNV secondary to chronic CSC were observed over 12 months. Males and females were equally distributed; mean age was 53 ± 14 years. Major demographic and clinical characteristics of the sample are shown in Table 1.

Mean BCVA increased significantly from 0.44 ± 0.35 at baseline to 0.57 ± 0.35 at month 1 (p=0.01), 0.6 ± 0.37 at month 3 (p=0.002), 0.61 ± 0.37 at month 6 (p = 0.002), and 0.58 ± 0.3 at month 12 (p = 0.01) (Fig. 1).

Mean CRT significantly decreased from 321.0 ± 90.0 μm to 260.0 ± 79.0 μm at month 1 (p = 0.04), 233.0 ± 42.0 μm at month 3 (p =0.0001), 229.0 ± 43.0 μm at month 6 (p = 0.0001), and 259.0 ± 93.0 μm at month 12 (p = 0.004) (Fig. 2).

Compared to baseline, mean SFCT decreased to 364.0 ± 186.0 μm at month 1 (p = 0.2), and significantly decreased to 340.0 ± 179.0 μm at month 3 (p = 0.04), 323.0 ± 165.0 μm at month 6 (p = 0.01), and 287.0 ± 124.0 μm at month 12 (p = 0.0002) (Fig. 3).

At month 12, complete resolution of SRF was observed in 18 eyes (75%). The mean number of injections over 12 months was 7.5 ± 1.4 with a range from 7 to 9. The mean interval between the last aflibercept injection and the final visit was 9.0 ± 4.1 weeks. During the study period, there were no cases of sudden vision loss, or FA or color fundus photography evidence of retinal pigment epithelial (RPE) or choroidal atrophy in eyes treated with aflibercept using treat-and-extend regimen for occult (type 1) CNV secondary to chronic CSC.

Discussion

Our prospective observational single-center study demonstrated that treat-and-extend treatment with intravitreal aflibercept contributed to an improvement in

Table 1. Major demographic and baseline clinical characteristics of patients with choroidal neovascularization secondary to chronic central serous chorioretinopathy

Characteristics	Mean ± standard deviation
Age, years	53.0 ± 14.0
Gender: Males, n (%) Females, n (%)	12 (50) 12 (50)
Symptom duration, days	44.0 ± 11.0
Baseline decimal best-corrected visual acuity	0.44 ± 0.35
Baseline mean central retinal thickness, μm	318.0 ± 101.0
Baseline mean subfoveal choroidal thickness, μm	398.0 ± 172.0

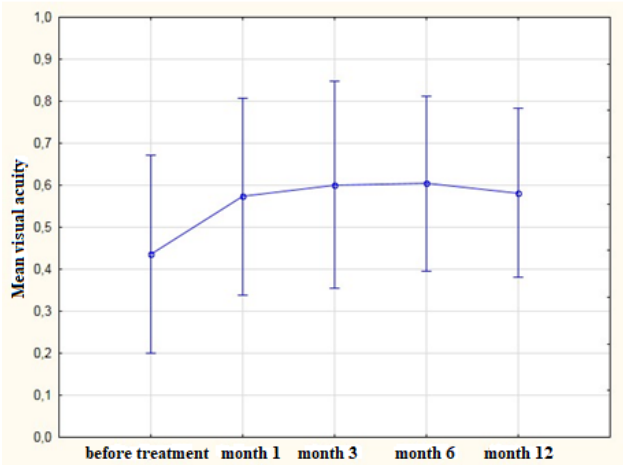

Fig. 1. Graph showing changes in mean visual acuity after initiation of aflibercept treatment in patients with choroidal neovascularization secondary to chronic central serous chorioretinopathy

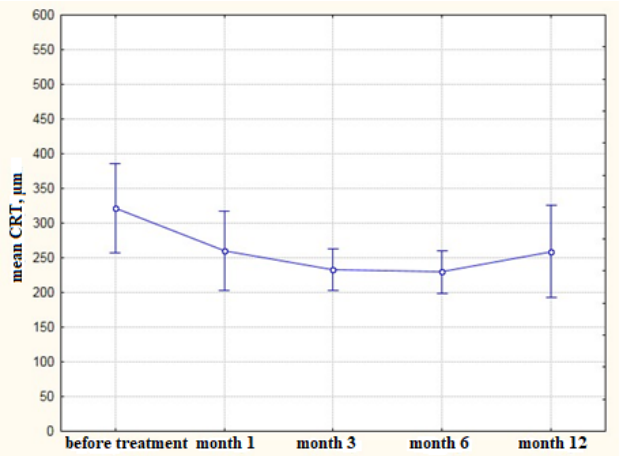

Fig. 2. Graph showing changes in mean central retinal thickness (CRT) after initiation of aflibercept treatment in patients with choroidal neovascularization secondary to chronic central serous chorioretinopathy

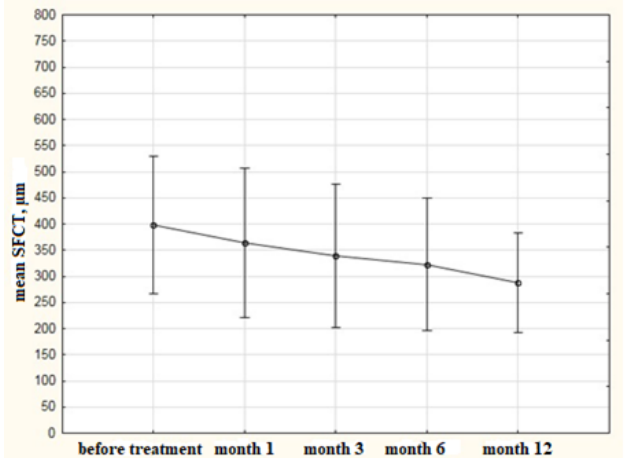

Fig. 3. Graph showing changes in mean subfoveal choroidal thickness (SFCT) after initiation of aflibercept treatment in patients with choroidal neovascularization secondary to chronic central serous chorioretinopathy

BCVA and reduction in CRT over 12 months in eyes with occult (type 1) CNV secondary to chronic CSC. In addition, it was demonstrated that treat-and-extend treatment with intravitreal aflibercept resulted in complete resolution of SRF in 75% of eyes. Moreover, no ocular or systemic side effect was observed during and after the treatment, and the mean number of intravitreal aflibercept injections over 12 months was 7.5 ± 1.4.

In the current study, the mean age of patients with CNV secondary to chronic CSC was 53 ± 14 years, which is comparable to reports of others. Yeo and colleagues [25] identified that older age, wider pigment epithelial detachment (PED) width at diagnosis, and recurrent episodes of CSC were independent risk factors for development of secondary CNV. They stressed that patients with these risk factors should be monitored to allow early detection and prompt treatment of secondary CNV. In a study by Schworm and colleagues [22], mean age of patients with CNV secondary to chronic CSC was 65 ± 8.3 years.

Multimodal fundus imaging (including OCTA) provides a promising CNV detection rate, secondary to chronic CSC, in a clinical setting [8]. In the current study, all patients with chronic CSC were diagnosed with type 1 CNV that proliferates between Bruch's membrane and the RPE. Fung and colleagues [5] used multimodal imaging and confirmed the predominance of type 1 CNV in patients with CSC. In a study by Schworm and colleagues [22], diagnosis of type 1 CNV was obtained by FA, indocyanine green angiography (ICGA), OCT and OCTA. They stress that neovascularization due to chronic CSC usually presents with type 1 CNV, which is known to show a weaker response to anti-VEGF compared with type 2 lesions. A study by Chhablani and colleagues [26] included 43 patients (46 eyes presenting with acute or chronic CSC associated with the presence of an active CNV as evidenced by OCT, ICGA, and FA; most of these

eyes were those with chronic CSC). Type 1 CNV (between the Bruch membrane and the RPE) was present in 20 eyes (43.4%), Type 2 (CNV between the RPE and the retina) in 25 eyes (54.3%), and 1 eye had suspected Type 3 CNV (intraretinal neovascularization). Lee and colleagues [27] identified clinical characteristics and risk factors of CNV in eyes with prior episode of CSC. CSC with SRF was confirmed by ICGA, FA, and OCT. On FA, classic type CNV was revealed in 23 (76.7%) eyes while occult type CNV was detected in 7 (23.3%) eyes. Studies [26] and [27], however, did not use OCTA in multimodal imaging.

There is no consensus on the standard treatment of CNV secondary to chronic CSC. Common treatment options include anti-VEGF therapy, PDT and their combination [18, 28]. In recent years, there has been an increase in studies advocating for monotherapy with various anti-VEGF agents for CNV secondary to chronic CSC [22, 26, 29].

The search for an optimal approach to anti-VEGF therapy for CNV secondary to CSC is still ongoing, with evaluation of efficacy and safety of various VEGF inhibitors and various intravitreal anti-VEGF treatment regimens. Konstantinidis and Mantel [29] reported on intravitreal ranibizumab treatment of 5 eyes with CNV related to chronic CSC. Each patient received an initial dose of 3 injections on monthly intervals. Indications for retreatment in each subsequent follow-up visit were persistent leakage from CNV shown on FA and/or presence of fluid on OCT (PRN regimen). Mean follow-up was 21 months (range, 19–24 months, SD: 1.9). The mean number of intravitreal injections administered for each patient was 10 (range, 5–16; SD: 4.6). The authors concluded that intravitreal ranibizumab appeared to be an effective treatment of CNV related to chronic CSC. However, residual intraretinal or subretinal fluid and increased choroidal permeability persisted.

In a study by Chhablani and colleagues [26], treatment for CSC associated with the presence of an active CNV consisted of intravitreal injection of bevacizumab, ranibizumab, or aflibercept. After obtaining informed consent, injection was given as per standard protocol. Mean number of anti-VEGF injections during the median follow-up of 19 months was 4.45 ± 4.1. Twenty-four eyes (52%) had visual improvement during follow-up. In 11 eyes (24%), vision did not change during the follow-up; however, the remaining 11 eyes (24%) had decrease in visual acuity. The authors concluded that anti-vascular endothelial growth factor therapy as a primary therapy for CNV secondary to CSC is safe and efficacious, without any serious adverse events.

Lai and colleagues [19] evaluated the efficacy and safety of ranibizumab 0.5 mg using an individualized PRN regimen in adult patients with CNV because of an uncommon cause enrolled in the 12-month MINERVA study. Overall, ranibizumab was effective in treating choroidal neovascularization of various etiologies with no new safety findings. The study findings support early initiation of treatment to achieve the best possible outcomes [19].

Jung and colleagues [20] retrospectively compared the efficacy of intravitreal injection of ranibizumab and aflibercept for patients with pachychoroid neovasculopathy. The term "pachychoroid neovasculopathy" has been introduced to describe type 1 neovascularization associated with choroidal thickening and/or dilated Haller vessels in the absence of characteristic age-related macular degeneration features. Pachychoroid neovasculopathy may be discovered as an incidental finding in patients with a history of CSC, and can ultimately progress to the development of polypoidal choroidal vasculopathy [30]. Fifty-four eyes were initially treated with 3 monthly loading injections of ranibizumab or aflibercept. There was no significant difference between the two groups in terms of visual improvement or decrease in central macular thickness. Aflibercept, however, was superior to ranibizumab in achieving dry macula and reducing choroidal thickness at 3 months [20].

Mao and colleagues [31] evaluated the efficacy and safety of conbercept (one intravitreal anti-VEGF injection of conbercept at the baseline followed by as-needed reinjection) for patients CSC. They concluded that intravitreal injection of conbercept may effectively reduce the central macular thickness (CMT) and improve the BCVA in chronic CSC in a short term of 6 months.

Schworm and colleagues [22] used another approach, an extended 6-month intravitreal anti-VEGF upload in CNV secondary to chronic CSC. Twenty-one patients with CNV secondary to chronic CSC received 6-monthly injections of ranibizumab or aflibercept (the mean interval between injections was 34 ± 3 days). Mean CRT decreased from 346 ± 61 to 257 ± 57 μm ($p < 0.01$) after the sixth injection while mean visual acuity improved from 0.65 ± 0.35 to 0.49 ± 0.29 (logMAR; $p < 0.01$). Of note, an extended upload of six as opposed to three injections yielded an additional mean CRT (280 ± 46 μm vs. 257 ± 57 μm, $p = 0.038$). In a study by Romdhane and colleagues [21], patients with CNV (OCTA evidence of type 1 CNV in 89% and type 2 CNV in 11% of eyes) secondary to chronic CSC received monthly injections of ranibizumab or aflibercept as needed. The anti-VEGF response was highly variable and often incomplete, suggesting that CNV was not solely responsible for the fluid accumulation. CNV may be inactive even in the presence of the SRF due to exudation in CSC. Therefore, SRF might be caused by the underlying pachychoroid and the CNV. As a result, an important treatment effect of anti-VEGF in pachychoroid disease may lie within the induction of choroidal thinning and reduction of choroidal hyperpermeability as opposed to sole fluid reduction [22].

In a study by Pitcher and colleagues [32], intravitreal aflibercept was well tolerated over a 6-month treatment course for chronic CSC without CNV, with no changes observed in visual acuity metrics, but with mean choroidal thickness decreased from 307 μm (SD = 72 μm) to 263 μm

(SD = 63 μm). In the current study, at 12 months, the mean SFCT was significantly lower than at baseline, indicating not only the occlusion of choroidal neovascular vessels, but also choroidal remodeling.

This study has some limitations. First, our sample size was relatively small due to the low incidence of CNV secondary to CSC. Second, we did not aim to review the OCT characteristics of the central retina for identification of treatment outcome predictors. Third, our study does not allow comparing various anti-VEGF agents for efficacy in CNV secondary to CSC, or determining the optimal treatment regimen.

Nevertheless, this study demonstrated that, intravitreal aflibercept in the treat-and-extend regimen resulted in a significant improvement in visual acuity in patients with CNV secondary to chronic CSC. In addition, in 75% of these patients, it resulted in complete SRF resolution with not only the occlusion of choroidal neovascular vessels, but also choroidal remodeling.

Conclusion

Treat-and-extend intravitreal aflibercept is an effective and safe approach for managing patients with occult (type 1) CNV secondary to chronic CSC, with functional and anatomical improvements at month 12. Further research is warranted with a larger sample size and longer duration to assess the efficacy and safety of a treat-and-extend aflibercept regimen as a treatment for CNV secondary to chronic CSC.

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Disclosures

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Abbreviations: *CNV, choroidal neovascularization; CRT, central retinal thickness;CSC, central serous chorioretinopathy; FA, fluorescein angiography; ICGA, indocyanine green angiography; OCT, optical coherence tomography; PDT, photodynamic therapy; PRN, pro re nata; RPE, retinal pigment epithelium; SD, standard deviation; SFCT, subfoveal choroidal thickness; SRF, subretinal fluid; VEGF, anti-vascular endothelial growth factor*