• Clinical Research •

Influence of combined eplerenone, aflibercept and nepafenac therapy on central serous chorioretinopathy

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Abstract

● **AIM:** To describe the influence of adding topical nepafenac to both; oral eplerenone and intravitreal aflibercept on serous foveal detachment in eyes with central serous chorioretinopathy (CSCR).

● **METHODS:** This retrospective cohort study included 31 eyes with non-resolving and recurrent CSCR that have been treated between 2015 and 2022 at Kasr Alainy Hospital. They were subdivided into Group A, which had been treated with a combination of systemic eplerenone, intravitreal aflibercept and topical nepafenac, and Group B, which had been treated with a combination of systemic eplerenone and intravitreal aflibercept (without topical nepafenac). Our outcome measures included changes in the best corrected visual acuity (BCVA), central subfield macular thickness (CMT) and serous detachment height (SDH) at baseline and at 2mo after treatment.

● **RESULTS:** Group A included 16 eyes. BCVA improved significantly from a logMAR of 0.62±0.44 to 0.42±0.47 (P=0.03), CMT decreased significantly from 401±61 to 301±100 μm, and SDH decreased significantly from 188±81 to 71±100 μm. Group B included 15 eyes. BCVA improved significantly from a logMAR of 0.68±0.39 to 0.55±0.62 (P=0.03), CMT decreased significantly from 411±39 μm to 334±92 μm, and SDH decreased significantly from 191±88 to 121±74 μm. There was a significant difference between changes in BCVA, CMT, and SDH between the two groups.

● **CONCLUSION:** Using topical nepafenac in combination with both systemic eplerenone, and intravitreal aflibercept may provide better results in the treatment of CSCR.

● **KEYWORDS:** central serous chorioretinopathy; aflibercept; eplerenone; nepafenac

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INTRODUCTION

Central serous chorioretinopathy (CSCR) is a macular disorder that involves serous detachment of the fovea (SFD), serous detachment of the retinal pigment epithelium (PED), and/or retinal pigment epithelial layer (RPE) atrophy. This is usually due to a defect in the RPE, which may be single or multiple. It occurs commonly in middle-aged males, especially type A smokers. A high cortisol level is associated with this disorder. It is commonly a self-limited disorder that resolves within 4mo (acute CSCR), with a good visual prognosis 90%-95%. Persistent or recurrent CSCR with RPE atrophy is considered chronic CSCR[1-5].

Classification of CSCR into acute and chronic types cannot be simply done based on duration of symptoms and SFD[1-5]. Daruich *et al*[6] proposed a more practical and detailed classification; which entails the following: acute resolving CSCR, acute non-resolving CSCR, recurrent CSCR, chronic active CSCR, and chronic inactive CSCR.

There is also no consensus for etiology of CSCR. However, a novel etiological classification has been proposed in 2022; including both exogenous and endogenous factors. Exogenous factors included: stress, drugs, and trauma. Endogenous factors included: pachysclera, vortex vein stasis, diabetes mellitus, hypertension, pregnancy, renal disease, and gastrointestinal reflux disease (GERD). Pathophysiology of CSCR was attributed to a pack of genetic, vascular, and immunological factors[3].

Treatment options include observation for acute cases; laser therapy for defects in RPE; threshold or subthreshold[7-11] mineralocorticoid receptor (MR) antagonists[12-18] photodynamic therapy (PDT)[9,11,19-20]; anti-vascular endothelial growth factor (anti-VEGF) agents[20-25]; topical nepafenac therapy[26-27]; oral ketoconazole treatment[28]; intravitreal metoprolol[29]; and brachytherapy[30].

MR antagonists, including spironolactone[16-17], and eplerenone, are used with controversial efficacy in CSCR[8-11,13]. Eplerenone has fewer side effects than spironolactone[12-16,18,31]. However,

eplerenone is associated with less resolution of macular detachment and little improvement of visual function.

Anti-VEGF agents, including bevacizumab[22], ranibizumab[23], and aflibercept[24-25], are used with some anatomical improvement. Aflibercept has been used in combination with PDT with some improvement in chronic CSCR[19-20].

Topical non-steroidal anti-inflammatory drugs (NSAIDs) have rarely been used for CSCR; and have achieved faster resolution of serous submacular fluid[26-27].

Single-modality treatment, or combination therapy that usually consists of laser treatment or PDT combined with an anti-VEGF agent, have been used for the treatment of CSCR, especially chronic CSCR.

However, there is no consensus for a gold standard protocol for treatment of CSCR[32]. Moreover, triple combination therapy using MR antagonists, anti-VEGF agent, and topical nepafenac has not been used before for CSCR[19,32].

Our study demonstrates a triple combination therapy that describes the influence of adding topical nepafenac to both; oral eplerenone and intravitreal aflibercept on serous foveal detachment in eyes with CSCR.

PARTICIPANTS AND METHODS

Ethical Approval This retrospective cohort study received approval from the Ethics Committee of Kasr Alainy Medical School (Cairo University) with the number (N-20-2023), and was registered at clinical trial.gov with the ID NCT05847049 on May 2023. All procedures fulfilled the Declaration of Helsinki. Written informed consent was obtained from each subject at the time of the intervention.

Patients This study included eyes that were diagnosed with CSCR and who received a combination treatment of systemic eplerenone, intravitreal aflibercept, with or without topical nepafenac from January 2015 to January 2022 at Kasr Alainy Hospital of Cairo University.

The treatment protocol for CSCR in our hospital consisted of systemic eplerenone, and intravitreal aflibercept until 2017. We started adding topical nepafenac eye drops to systemic eplerenone, and intravitreal aflibercept in 2018.

Diagnosis of Acute Central Serous Chorioretinopathy Presence of serous detachment of the neurosensory retina with or without RPE detachment on optical coherence tomography (OCT; Spectralis, Heidelberg, Germany), and/or evidence of fluorescent leakage on fundus fluorescein angiography (FFA; Spectralis, Heidelberg, Germany).

Definition of Chronic Central Serous Chorioretinopathy Presence of RPE atrophy (detected as a thinned RPE layer with reverse shadowing of the underlying choriocapillaris on OCT). Chronic active CSCR refers to chronic CSCR with the presence of SFD, while chronic inactive CSCR refers to chronic CSCR in absence of SFD.

Inclusion Criteria 1) Age>18y; 2) acute CSCR more than 4mo duration (acute non-resolving) 3); recurrent CSCR of any duration; 6) a follow-up period at least 2mo.

Exclusion Criteria 1) Chronic CSCR (whether active or inactive), 2) acute CSCR less than 4mo duration, 3) follow-up period less than 2mo, 4) CSCR accompanied by other eye diseases, such as AMD, polypoidal choroidal vasculopathy, glaucoma, or ocular trauma; 5) treatment with any other modality or observation, 6) pregnancy, 7) cases with evident choroidal neovascular membrane (CNVM).

The patients were divided into 2 groups (A and B). Group A included eyes that had been treated with a combination of systemic eplerenone, intravitreal aflibercept and topical nepafenac, and Group B included eyes that had been treated with a combination of systemic eplerenone, intravitreal aflibercept (without topical nepafenac).

All patients received intravitreal injections of aflibercept (2 mg/0.05 mL; Eylea, Bayer Schweiz AG, Zurich, Switzerland) under sterile conditions. At the same time; the patients received 50 mg of oral eplerenone tablets (Tensopleron®, Global pharmaceutical industries, 6th October city, Egypt); 50 mg daily for 1mo, and then 25 mg daily for 3mo.

Group A eyes received in addition; topical nepafenac 0.1% eye drops (Nevanac, Alcon Novartis Pharma AG, Basel, Switzerland) twice daily for 4mo.

The data collected included: age, gender, any systemic disease, smoking status, best corrected visual acuity (BCVA), central subfield macular thickness (CMT), serous detachment height (SDH). CMT and SDH were measured by OCT (Spectralis, Heidelberg, Germany). SDH was measured at the point of maximum height, and the same point was used to make the measurements during follow-up. BCVA was measured using a decimal chart and then converted into logMAR values for statistical purposes. All data were collected from the measurements that had been performed at baseline and at 2mo.

Statistical Analysis All statistical analyses were performed using StatPlus software (StatPlus: mac LE, build 6.1.2/Core v6.1.0, AnalystSoft Inc., Walnut, CA, USA). The baseline characteristics were analyzed using descriptive analysis. Comparison between outcome measures; at baseline and at final follow-up; were done using a sample *t*-test. The Chi-square test was used to compare between categorical variables. The BCVA was converted into the logMAR value for statistical purposes. Statistical significance was set at a P value less than 0.05.

RESULTS

We identified 31 eyes in our study after applying both the inclusion and exclusion criteria. Group A included 16 eyes that had been treated with a combination of systemic eplerenone, intravitreal aflibercept and topical nepafenac, between 2018

and 2022. Group B included 15 eyes that had been treated with a combination of systemic eplerenone and intravitreal aflibercept (without topical nepafenac) between 2015 and 2017.

The baseline demographic data and clinical characteristics are summarized in Table 1. They showed a statistically insignificant difference between both groups.

During the follow-up period, no severe systemic or ocular adverse events were noted relevant to the therapeutic agents used in the study such as, vitreous hemorrhage, retinal detachment, uveitis, or endophthalmitis.

Group A Changes BCVA improved significantly from a logMAR of 0.62±0.44 at baseline to a logMAR of 0.42±0.47 at 2mo (P=0.03). There was a statistically significant reduction in CMT from 401±61 μm at baseline to 301±100 μm at 2mo (P=0.02). SDH decreased significantly from 188±81 μm at baseline to 71±100 μm at 2mo (P=0.02).

Group B Changes BCVA improved significantly from a logMAR of 0.68±0.39 at baseline to a logMAR of 0.55±0.62 at 2mo (P=0.03). There was a statistically significant reduction of CMT from 411±39 μm at baseline to 334±92 μm at 2mo (P=0.04). SDH decreased significantly from 191±88 μm at baseline to 120±74 μm at 2mo (P=0.04).

Changes in the Central Macular Thickness in Both Groups There was a statistically significant greater reduction in CMT in group A (120±22 μm) than in group B (82±14 μm; P=0.02). Most of the eyes in both groups showed less than 100 μm reduction in CMT at 2mo: 9 eyes in group A (56.3%), and 11 eyes in group B (73.3%). We cannot confirm that more eyes showed >200 μm reduction in CMT in group A than in group B (3 eyes in group A, 1 eye in group B, P=0.32). The details are displayed in Table 2.

Changes in the Serous Detachment Height in Both Groups There was a statistically significant greater reduction in the SDH in group A (119±24 μm) than in group B (78±17 μm; P=0.04). Most of the eyes in both groups showed 100-200 μm reduction in SDH at 2mo; 9 eyes in group A (56.3%), and 8 eyes in group B (53.3%). We cannot confirm that more eyes showed >200 μm reduction in SDH in group A than in group B (2 eyes in group A, 1 eye in group B, P=0.88; Table 3).

Complete resolution of subretinal fluid was observed in 8 eyes in group A (50%), and in 5 eyes in group B (33.3%). There was a significantly greater incidence of complete resolution of subretinal fluid in group A than in group B at 2mo (P=0.04; Table 3, Figures 1 and 2).

Changes in the Best Corrected Visual Acuity in Both Groups There was a nonsignificant difference in the number of lines of improvement in BCVA between the two groups (P=0.18); group A showed 1.75±1.30 lines of improvement compared to 1.33±1.23 lines of improvement in group B. We observed 3 or more lines of improvement of BCVA in 7 eyes in group A (43.7%), and in 4 eyes in group B (26.7%); however, it was not statistically significant (P=0.21; Table 4).

Table 1 Baseline demographic and clinical data for both groups

Items	Group A (n=16)	Group B (n=15)	P
Age	42±8	44±7	0.34
Male to female	13:3	12:3	0.89
Smoking	11 (68.8%)	10 (66.7%)	0.72
Hypertension	9 (56.3%)	7 (46.7%)	0.54
BCVA (logMAR)	0.62±0.44	0.68±0.39	0.23
CMT	401±61	411±39	0.19
SDH	188±81	191±85	0.28
Non-resolving acute CSCR	10 (62.5%)	9 (60%)	0.886
Recurrent acute CSCR	6 (37.5%)	6 (40%)	
Duration of symptoms (mo)			
Non-resolving acute CSCR	5.5±0.7	5.7±0.9	0.684
Recurrent acute CSCR	2.8±1.1	2.6±1.3	0.804

BCVA: Best corrected visual acuity; CMT: Central subfield macular thickness; SDH: Serous detachment height; CSCR: Central serous chorioretinopathy.

Table 2 Reduction in CMT

Reduction in CMT (μm)	Group A	Group B	P
<100	9	11	0.31
100-200	4	3	0.74
>200	3	1	0.32

CMT: Central macular thickness.

Table 3 Reduction in SDH

Reduction in SDH	Group A (n=16)	Group B (n=15)	P
Complete resolution	8	5	0.04
<100 μm reduction	5	6	0.61
100-200 μm reduction	9	8	0.87
>200 μm reduction	2	1	0.58

SDH: Serous detachment height.

Table 4 Change in BCVA

Lines of improvement of BCVA	Group A (n=16)	Group B (n=15)	P
3 or more lines	7	4	0.21
No improvement	4	5	0.83
1-2 lines	5	6	0.76

BCVA: Best corrected visual acuity.

DISCUSSION

Our study demonstrated the outcome of using a special combination therapy for CSCR, which consisted of intravitreal aflibercept, oral eplerenone and topical nepafenac. Our study revealed a remarkable reduction in serous detachment over a short duration of 2mo.

Using topical nepafenac, together with eplerenone and aflibercept; in our study achieved greater reduction in both macular thickness and serous detachment, than using only a

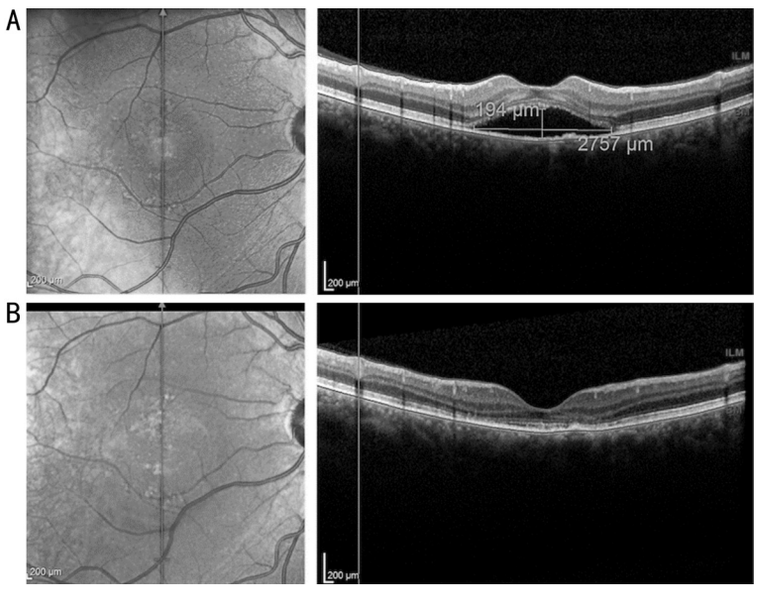

Figure 1 OCT and infra-red image of a case of CSCR in group A that achieved a complete resolution of subretinal fluid A: A baseline serous foveal detachment with a SDH of 194 μm; B: A complete resolution of subretinal fluid at 2mo. OCT: Optical coherence tomography; CSCR: Central serous chorioretinopathy; SDH: Serous detachment height.

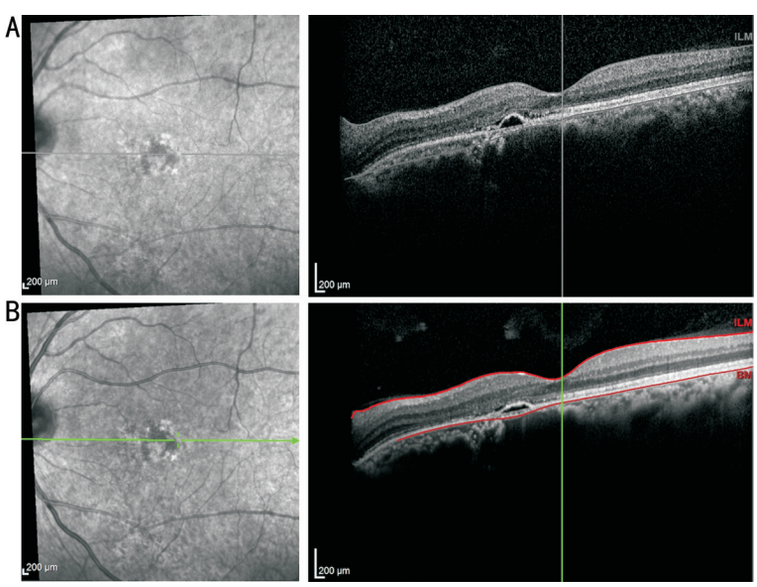

Figure 2 OCT and infra-red images of a case of CSCR in group B that achieved a partial resolution of subretinal fluid A: A baseline parafoveal serous detachment; B: A partial reduction in the SDH at 2mo.

combination of eplerenone and aflibercept (without nepafenac). No previous studies have been performed on this combination therapy for treatment.

Eplerenone has been used for treatment of CSCR with generally unfavorable results, even though it has fewer side effects than spironolactone therapy. It has been used as a monotherapy, either as compared to a placebo[18], or a non-treatment group[16], or as compared to micropulse laser treatment group[6].

Eplerenone tablets 50 mg/d for 3mo were used for the treatment group, while a placebo was used for the control group. There was a significant more reduction in subretinal fluid (SRF) in the placebo group at 3mo, compared to the eplerenone group (30.8%, 23%, respectively)[18]. However, this can be explained by the inclusion of chronic cases of CSCR in the study, and insufficient response with eplerenone as a monotherapy. Acute non-resolving CSCR cases responded well to oral eplerenone, with significant reduction of SRF in 7 patients at 1mo. However, there was no control group for comparison[16]. Toto *et al*[7] reported complete resolution of SFD in 66.7% of eyes with chronic CSCR on eplerenone therapy compared to 55.6% of eyes for which subthreshold macular laser was performed, after 3mo of follow-up.

The eplerenone protocol used in our study differed from that used in previous studies. We started with a 50 mg daily dose for 1mo and then a 25 mg daily dose for 3mo. Our endpoint

was at 2mo. The VICI study used a different protocol, starting with a 25 mg dose for 1wk then a 50 mg dose for up to 12mo[33]. Schwartz *et al*[18] used 50 mg daily dose throughout their study on cases of chronic CSCR for 3mo. Bousquet *et al*[31] started with 25 mg daily for 1wk, followed by 50 mg daily for 3mo. They reported significant reduction of SRF at 1mo and at 3mo. No serious side effects were reported by any of these protocols; whether with aggressive dose[18] or with cautious buildup of the dose[32].

We assume that starting with a higher dose in our study; as a loading dose and then reducing it to a half dose as a maintenance dose; would be more effective than the reverse protocol. Our assumption was based on the absence of serious side effects from previous data about eplerenone[12-16,18,33].

Intravitreal aflibercept has been used with an initial remarkable transient resolution of subretinal fluid in the first month, followed by rebound increase in subretinal fluid between the first and second month[24]. Jung *et al*[24] reported a rebound increase in SRF in 40% of eyes at 2 and 3mo of follow-up. Central subfoveal thickness decreased from a baseline average 445 μm to an average 276 μm at 2mo, then to an average 289 μm at 3mo respectively.

The explanation for this response is a transient reduction of leakage from either hyperpermeable choroidal vasculature, or a presumed nonevident choroidal neovascular membrane that may be concurrent with CSCR, and the rebound increase is due to cessation of the response to aflibercept[18-20,23-24].

No rebound increase in subretinal fluid was observed in both groups of our study during the same period of 2mo, which can be explained by the synergistic subretinal fluid reduction effect of the other 2 components of the triple therapy (eplerenone and nepafenac).

Topical nepafenac has been used for CSCR with favorable results. Complete resolution of subretinal fluid was observed by Alkin *et al*[26] in 82.3% of eyes after 6mo, compared to 42.8% in the control untreated eyes. Nepafenac 0.1% eye drops were instilled 3 times daily for cases with acute CSCR; initially for 4wk that extended till complete resolution of SRF up to 6mo[26]. Significant reduction in CMT was observed in that study; from a baseline average 349 μm, to an average 257 μm at 1mo, 248 μm at 3mo, then to 221 μm at 6mo of follow-up respectively[26]. However, the study was done on eyes with acute CSCR irrespective to the duration of symptoms, and the follow-up was extensively longer than expected for spontaneous resolution (6mo, compared to 4mo for spontaneous resolution)[26].

Bahadorani *et al*[27] reported 196 μm reduction in CMT at 4-5wk after nepafenac therapy. Eye drops were instilled 4 times daily. Resolution of subretinal fluid was observed in 64.3% of eyes over the same period of 4-5wk, which can be considered as a rapid effective response.

We used nepafenac based on assumptions from previous studies about a prostaglandin-related choroidal inflammation as a contributing factor to the pathogenesis of CSCR[3,26].

Role of nepafenac in CSCR has been explained through a triad of: anti-inflammatory effect, anti-aldosterone effect, and an anti-coagulant effect[27]. Topical nepafenac is converted into a metabolically active metabolite “Amfenac” in retina, choroid, and ciliary epithelium; which readily penetrates target retinal tissue, and subsequently exerts its therapeutic effects on subretinal fluid[26]. Anti-inflammatory effect of nepafenac occurs through reduction of prostaglandins; which highlights an underlying inflammatory mechanism for CSCR. Aldosterone is reduced by nepafenac therapy; which maybe congruent to the therapeutic effects of MR antagonists (spironolactone, and eplerenone)[27].

Nepafenac protocol in our study is similar to the other studies concerning the 0.1% concentration of eye drops; as this is the common commercially available product (Nevanac, Alcon Novartis Pharma AG, Basel, Switzerland). However, the daily dosage and duration of therapy were different in our study. In our study, topical nepafenac was used only 2 times daily over 2mo (the endpoint of evaluation was 2mo). Alkin *et al*[26] used nepafenac 3 times daily for a very long duration up to 6mo, while Bahadorani *et al*[27] used nepafenac 4 times daily for a very short duration of 4-5wk. We assumed that we can achieve a favorable response with just 2 daily doses than 3 or 4 doses; based on our experience with other macular oedema disorders, and on the triple combination therapy that we used in our study.

We observed a complete resolution of subretinal fluid in 50% of eyes and an average 120 μm reduction in CMT. We assume that the rapid resolution effect while using a lower dose of topical nepafenac 0.1%; in our study; may be due to the synergistic effect of triple combination therapy (together with systemic eplerenone, and intravitreal aflibercept).

We started our study protocol with an intravitreal aflibercept injection, an initial high dose of eplerenone tablets (50 mg) for 1mo, and a twice daily dose of nepafenac eye drops; to act as a loading dose that achieved an initial synergetic effect on CSCR. Then, we continued with a half dose of eplerenone, and a twice daily dose of nepafenac as a maintenance dose over the next month of the study.

The control group in our study included eyes that were treated with 2 components of the triple therapy in the treatment group (aflibercept and eplerenone). We did not include for the control group eyes that were observed or treated by any modality other than eplerenone and aflibercept.

To our knowledge, topical nepafenac for CSCR had been reported only twice (2013, and 2019), compared to many

reports about eplerenone and aflibercept. Moreover, we started adding topical nepafenac to both; eplerenone and aflibercept; for CSCR in 2018 in our practice in Kasr Alainy Medical School (Cairo University). This explains the design of both cohorts of the study.

The endpoint of our study was at 2mo, even though the treatment had been extended to an additional 2mo (a total of 4mo). Our aim was to assess the speed of resolution of subretinal fluid before the expected time of approximately 4mo since the onset of symptoms or treatment even for non-resolving cases[1-5]. This is because we included in our study eyes with either; non-resolving acute CSCR, or with a recurrent attack of CSCR. We excluded chronic cases of CSCR, and acute CSCR with less than 4mo duration of symptoms. We assumed that the enrolled cases wouldn't need further 4mo of therapy to achieve resolution of subretinal fluid; thus; we restricted our follow-up to just 2mo, to evaluate the speed of recovery under triple therapy more precisely.

Our study relied on OCT findings, and duration of symptoms at baseline to include patients with non-resolving or recurrent acute CSCR with subretinal fluid and without RPE atrophy. Thus; we excluded eyes with chronic CSCR. This would eliminate all probable confounding variables in the study. We recommend further studies on our combination therapy, and other combinations, involving larger number of eyes to assist in formulating guidelines for the management of CSCR.

In conclusion, using topical nepafenac in combination with both systemic eplerenone, and intravitreal aflibercept may provide better results in the treatment of CSCR.

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Availability of Data and Materials: The datasets used during the current study are available from the corresponding author upon reasonable request.

Conflicts of Interest: Ewais WA, None; **Samy Ali L,** None; **Aboalazayem F,** None.

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