Original Article

Effect of Eplerenone Treatment in Patients with Central Serous Retinopathy: A Double-Blind Randomized Clinical Trial

Mohammadreza Akhlaghi[1], Alireza Dehghani[1], Farzan Kianersi[1], Mohammad Reza Khalili[2], Mohammad Tohidi[1], Hamidreza Jahanbani-Ardakani[2]

[1]Isfahan Eye Research Center, Department of Ophthalmology, Isfahan University of Medical Sciences, Isfahan, Iran, [2]Department of Ophthalmology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

Abstract

Purpose: To evaluate the efficacy of eplerenone in central serous chorioretinopathy (CSCR) patients in a clinical trial design.

Methods: In this double-blind clinical trial, naive acute CSCR patients were divided into two groups: treatment with eplerenone 25 mg daily in the 1st week followed by 50 mg for the next 3 weeks and placebo group. Best-corrected visual acuity (BCVA), central macular thickness (CMT), macular volume (MV), and choroidal thickness (CT) were measured before and after 1 month of the intervention using the optical coherence tomography technique.

Results: Thirty-one CSCR (male: 23, female: 8) and 25 CSCR patients (male: 18, female: 7) with the mean age of 35.65 ± 5.94 and 37.08 ± 6.41 years were recruited and divided randomly into treatment and placebo groups, respectively. BCVA improved significantly in the treatment group (from 0.28 ± 0.26 to 0.11 ± 0.14, $P = 0.002$) compared with the placebo group (from 0.31 ± 0.26 to 0.21 ± 0.14, $P = 0.052$). Although CT, CMT, and MV improved significantly in each group, there were no significant differences between the groups.

Conclusion: In this study, we found favorable short-term clinical effects of eplerenone in acute CSCR patients, showing the pivotal role of mineralocorticoid receptors in the retina.

Keywords: Best-corrected visual acuity, Central macular thickness, Central serous chorioretinopathy, Choroidal thickness, Eplerenone

Address for correspondence: Hamidreza Jahanbani-Ardakani, Department of Ophthalmology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran.
E-mail: hamidreza_jahanbaniardakani@yahoo.com
Submitted: 10-Jan-2022; **Revised:** 03-Nov-2023; **Accepted:** 03-Nov-2023; **Published:** 16-Oct-2024

Introduction

Central serous chorioretinopathy (CSCR) is the fourth common retinal disease characterized by detachment of the retinal neurosensory layer due to increased permeability of the choroidal vasculature tissue, resulting in accumulation of serous subretinal fluid between the neurosensory retina and retinal pigmented epithelium.[1] CSCR mostly affects young individuals in their working age with considerable male preponderance (it occurs 5 times more in men than females). Its presentation depends on the location and amount of serous subretinal fluid.[2] Although some environmental and genetic factors have been proposed in CSCR development, no exact etiology has been identified.[1,3] Frequently, CSCR affects both eyes and usually resolves spontaneously after 3 months of the attack.[4]

Since the first description of CSCR in 1866,[5] there has been controversy regarding its pathophysiology and effective treatment. Many therapeutic strategies have been suggested, but definitive treatment is still a subject of ongoing research. Recent studies have emphasized the role of mineralocorticoids in the disease pathogenesis. However, clinical randomized trials have reported controversial results on mineralocorticoids (including eplerenone) administration

Access this article online

Quick Response Code:

Website: https://journals.lww.com/joco

DOI: 10.4103/joco.joco_13_22

How to cite this article: Akhlaghi M, Dehghani A, Kianersi F, Khalili MR, Tohidi M, Jahanbani-Ardakani H. Effect of eplerenone treatment in patients with central serous retinopathy: A double-blind randomized clinical trial. J Curr Ophthalmol 2024;36:61-5.

in the treatment of CSCR patients.[6-20] These controversial reports may be due to different types of methodology such as different doses of drug and duration of follow-up. In the current study, we aimed to assess clinical and anatomical outcomes of eplerenone administration in an acute episode of CSCR.

Methods

This present study was conducted as a double-blind randomized placebo-controlled clinical trial at Feiz Hospital, affiliated with the Isfahan University of Medical Sciences, Isfahan, Iran, from September 2019 to October 2020. The protocol of the study was in agreement with the tenets of Declaration of Helsinki and was approved by Ethics Committee of Isfahan University of Medical Sciences, Isfahan (ID: IR.MUI.MED.REC.1397.242) and Iranian registry of clinical trials (Trial registration number: IRCT20180825040860N1; URL of trial registry record: https://en.irct.ir/trial/33527). All the patients signed the written consent form before any intervention.

All of the patients with acute episode of CSCR diagnosed by experienced ophthalmologists (retina fellowships) based on clinical and imaging findings were considered eligible for participation. Patients aged 18–60 years with the episode of acute CSCR during the recent 3 months were eligible for inclusion. Our exclusion criteria were (1) patients with any systematic diseases including diabetes mellitus, liver and kidney disorders, etc., (2) patients under treatment with corticosteroids, (3) previous history of retinal diseases, uveitis, glaucoma, choroidal neovascularization, polypoidal choroidal vasculopathy, and hyperkalemia, (4) history of ocular trauma or surgery, and (5) history of any previous treatment for CSCR such as photodynamic therapy or antivascular endothelial growth factor therapy.

Patients were randomly allocated into two groups: Group 1 received oral eplerenone (Inspra; Pfizer, Paris, France) and Group 2 received placebo treatment. Patient randomization was done by 1:1 eplerenone: placebo ratio using computer-generated numbers, and an independent ophthalmology attending coordinated the randomization. The group allocation was masked for patients and researchers of the present study.

In the treatment group, eplerenone 25 mg was administered daily during the 1st week followed by a 50 mg daily dose for the next 3 weeks. The placebo group was administered a placebo drug with the same content and color to eplerenone and was followed as same as the other group. All the participants were examined comprehensively before the beginning of the intervention using a Snellen chart, slit-lamp ophthalmoscopy, fundoscopy, fluorescein angiography, and optical coherence tomography (OCT) (Heidelberg Spectralis, Heidelberg, Germany). We recorded best-corrected visual acuity (BCVA) (converted to logMAR), central macular thickness (CMT), macular volume (MV), and choroidal thickness (CT) before and following 1 month of eplerenone administration. The MV, CMT, and CT parameters were measured using OCT machine (Heidelberg Engineering, Heidelberg, Germany), as described previously.[8,16] In brief, the MV was measured as the sum of the volumes of nine sections described in the Early Treatment Diabetic Retinopathy Study. The nine sections volume was calculated based on the following formula:

$$\text{MV: } \pi\left[\frac{A1}{4000}+\frac{12(B1+B2+B3+B4)}{48875}+\frac{17\,(C6+C7+C8+C9)}{39000}\right]$$

Furthermore, the CMT was measured using a macular map, and CT was measured manually using an enhanced-depth imaging technique. The primary study endpoint was mean changes of CMT after 4 weeks of eplerenone therapy or placebo. Secondary outcomes were mean changes of MV, CT, and BCVA.

Statistical analysis

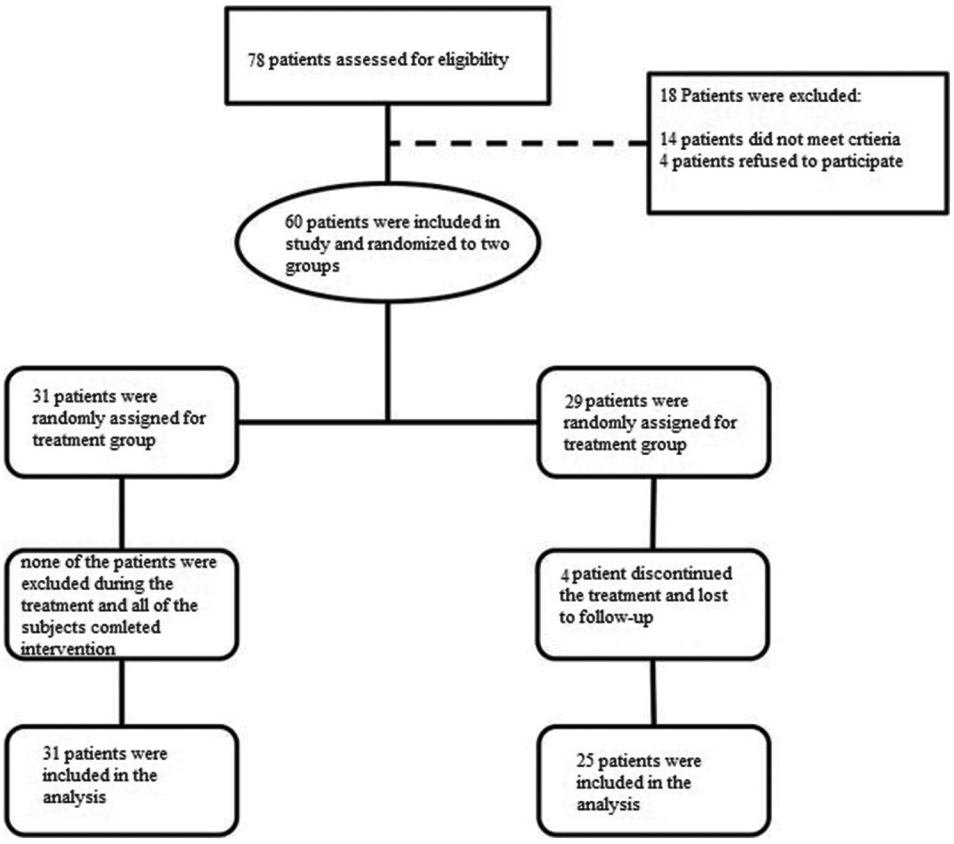
Data analysis was carried out using SPSS version 22 (IBM, Chicago, USA). The normality of data was assessed by Kolmogrov–Smirnov test. Repeated measures test was used to compare anatomical and clinical outcomes of the study at baseline and after the intervention between the groups. In addition, we used a paired sample *t*-test or Wilcoxon test for comparing the baseline and postintervention data within each group. All of the *P* values were reported two-tailed, and a $P < 0.05$ was considered as the threshold of significance.

Results

In this prospective interventional double-blind clinical trial, 56 patients with acute episodes of CSCR were enrolled [Flowchart 1]. Patients were divided into two groups: 31 patients (including 23 males and 8 females) in the treatment group and 25 (including 18 males and 7 females) in the placebo group with a mean age of 35.65 ± 5.94 and 37.08 ± 6.41 years, respectively. At baseline, there was no statistically significant differences between the groups regarding CT, CMT, MV, and BCVA ($P = 0.291$, $P = 0.089$, $P = 0.572$, and $P = 0.556$, respectively). After 1 month, a significantly better mean visual acuity (VA) was recorded in the treatment group ($P = 0.011$). However, our results did not show favorable outcomes regarding the central macula thickness, CT as well as MV in the treatment group compared to the placebo group ($P = 0.819$, $P = 0.477$, and $P = 0.450$, respectively) [Table 1]. Further analysis showed 11 CSCR patients in the treatment group with a final VA of 20/20, while there were only 4 patients with a final VA 20/20 in the placebo group. None of the patients who received eplerenone experienced any adverse effects such as hyperkalemia, dizziness, or other previously reported effects. Furthermore, no CSCR patients experienced new lesions during 3 months of the intervention.

Discussion

In the current research, we assessed eplerenone effects on



Flowchart 1: Diagram of participant's selection and allocated groups

anatomical and clinical outcomes in patients with acute CSCR. VA improvement was found in the treatment group compared with the placebo group. We observed a significant decrease in CMT, CT, and MV after 1 month in both groups. However, in anatomical items, including CMT, CT, and MV, no significant difference was found between the groups.

Our results showed improvement of VA in both treatment and placebo groups after 1 month of receiving eplerenone in comparison to baseline VA ($P = 0.002$ and $P = 0.052$, respectively). Many previous studies, in line with our results, have also shown improvement in VA after eplerenone administration.[1,7,8,10-12,14,16,17] Borrelli *et al*. reported the effects of eplerenone in 50 CSCR patients. The patients' BCVA improved from 0.20 ± 0.14 at baseline to 0.12 ± 0.13 at 3 months and 0.10 ± 0.12 at 12 months after eplerenone treatment ($P < 0.0001$ for both comparisons). In addition, in the present study, 11 CSCR patients in the treatment group showed 20/20 VA, while only 4 patients in the placebo group had 20/20/VA at the end of the study. In the same line with our study, Venkatesh *et al*. reported 3-month outcomes of eplerenone treatment in 58 CSCR patients. They found significant improvement in VA in both groups. However, VA changes were not significantly different between the groups.[21] In contrast, there are some studies reporting nonsignificant improvement in VA after eplerenone treatment.[6,13,22,23] In a recently published randomized double-blind multicenter study on 114 CSCR patients, the researchers did not detect significant improvement of VA in the treatment group compared with the placebo group ($P = 0.24$).[6] In another study, Petkovsek *et al*. investigated the efficacy of eplerenone on 100 eyes of 83 CSCR patients 1, 2, and 3 years after initiation of eplerenone. At none of these time points, authors found significantly better VA compared with baseline measurements.[22] In a recent study on 13 CSCR patients, no significant improvement in VA was detected after 1 month of eplerenone therapy.[23] Although our results did not reveal a significant difference in anatomical items between the groups after 3 months of intervention, such considerably better BCVA in the treatment group may be attributed to eplerenone effects on choroidal morphology and vasculature. A recently published study by Toto *et al*., shown a significantly reduced choroidal vascularity index was shown after eplerenone treatment, and this may indicate the substantial role of mineralocorticoid antagonists in recovery of choroidal morphology.[24] As the current research was conducted on CSCR patients in acute phase of the disease and spontaneous regression of the disease was expected in this period, we hypnotized that finding significant effects of eplerenone on anatomical items may need more time.

In this study, we found significantly lower CMT after 1 month of eplerenone as well as placebo treatment ($P < 0.001$). Similarly, Moein *et al*. reported similar findings on CMT in their study on 13 CSCR patients.[9] In the same line with our

Table 1: Clinical and anatomical data of patients, before and after eplerenone treatment

	VA (before)	VA (after)	*P* (within groups)	CT (before)	CT (after)	*P* (within groups)	CMT (before)	CMT (after)	*P* (within groups)	MV (before)	MV (after)	*P* (within groups)
Patient	0.28±0.26	0.11±0.14	0.002	514.87±124.20	407.06±118.74	<0.001	528.55±106.77	391.52±110.30	<0.001	254.90±133	115.84±118.14	<0.001
Control	0.31±0.26	0.21±0.14	0.052	481.44±106.32	385.52±102.94	0.004	482.84±86.16	384.88±103.33	<0.001	234.44±134.66	139.64±123.77	0.005
P (between groups)	0.556	0.011	-	0.291	0.477	-	0.089	0.819	-	0.572	0.450	-

VA: Visual acuity, CT: Choroidal thickness, CMT: Central macular thickness, MV: Macular volume

results, Schwartz *et al*. recorded a significant decrease in CMT after 3 months of eplerenone administration, while there was no significant difference with the placebo group at any time points of the follow-up.[10] In line with our findings, Bosuquet and associates documented a significant decrease in CMT in patients receiving eplerenone after 3 months compared to the baseline data.[11] In agreement with these findings, there are several studies reporting a significant decrease in CMT after eplerenone treatment.[1,7,8,10,13,17,25] In a recently published study from Pakistan, in agreement with our results, authors showed a significant decrease in CMT after 1 month of eplerenone administration in CSCR patients.[23]

Interestingly, Cakir *et al*. showed the association between CMT decrement and BCVA improvement in CSCR patients who received eplerenone.[13] On the contrary, Ghadiali *et al*. did not find a significant change in CMT after 12 months of eplerenone administration.[15]

Our results showed a significant decrease in MV in both groups; however, there was no significant difference between the groups at 1-month follow-up. Similar to our finding, Chin *et al*. found a decrease in MV after eplerenone administration in patients with refractory CSCR.[26] As there are few studies on the effect of eplerenone on MV, further studies are recommended to be conducted in this regard.

In the current research, we found a significantly lower CT after the intervention in both groups; however, the difference between the groups did not reach a significant level. In line with our results, Zucchiatti *et al*. evaluated the effects of eplerenone treatment versus observation in 15 and 12 eyes, respectively, and found a significantly decreased CT in the treatment group. However, they did not find any significant difference regarding CT changes in the control group after 3 months. They suggested that these changes in CT could be due to the eplerenone effect on the mineralocorticoids receptors of choroidal vessels.[8] However, in the current study with a larger sample size, changes in CT between the groups were not significant. Furthermore, Venkatesh *et al*. reported similar results to our findings. They detected considerable changes in CT after 3 months in both treatment and placebo groups.[21] This significant decrease in CT in both groups might be attributed to the spontaneous resolution of CSCR in the acute phase occurring in most patients. Similarly, Schwartz *et al*. reported a nonsignificant change in CT in the eplerenone treatment group compared with the placebo group. However, in contrast to our findings, they did not detect any considerable CT changes within the groups after eplerenone administration.[10]

Based on the findings of our study, prescribing eplerenone in the acute phase of CSCR disease could improve BCVA of patients. Although anatomical changes were also promising, these changes were not superior to the measurements obtained from the placebo group. Pitfall of the present study was short time follow-up of participants and lack of structural OCT imaging leading to the probable loss of subtle anatomical changes.

As there are few studies investigating the effects of mineralocorticoids antagonist receptor agents in the acute phase of CSCR, there is a demand for further studies to assess the efficacy of eplerenone in functional as well as anatomical parameters in patients with CSCR.

In conclusion, our results showed the significant effect of eplerenone on BCVA in CSCR patients. Although significant changes in anatomical parameters including CT, CMT, and MV were obtained, these outcomes were not superior to placebo. As the patients could tolerate eplerenone well, and there were scarce adverse effects, we suggest eplerenone alongside other therapeutic plans in CSCR. Future studies evaluating more items including retinal pigmented epithelium, external limiting membrane, and subretinal fluid changes are recommended to be conducted to show the efficacy of eplerenone in acute CSCR.

Acknowledgment

This study was funded by the Isfahan University of Medical Sciences, Isfahan, Iran Authors would like to thank Ms. Pegah Noorshargh for his kind help.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Daruich A, Matet A, Dirani A, Bousquet E, Zhao M, Farman N, *et al.* Central serous chorioretinopathy: Recent findings and new physiopathology hypothesis. Prog Retin Eye Res 2015;48:82-118.
2. Gemenetzi M, De Salvo G, Lotery AJ. Central serous chorioretinopathy: An update on pathogenesis and treatment. Eye (Lond) 2010;24:1743-56.
3. Schellevis RL, van Dijk EH, Breukink MB, Altay L, Bakker B, Koeleman BP, *et al.* Role of the complement system in chronic central serous chorioretinopathy: A genome-wide association study. JAMA Ophthalmol 2018;136:1128-36.
4. van Rijssen TJ, van Dijk EH, Yzer S, Ohno-Matsui K, Keunen JE, Schlingemann RO, *et al.* Central serous chorioretinopathy: Towards an evidence-based treatment guideline. Prog Retin Eye Res 2019;73:100770.
5. Von Graefe A. Ueber centrale recidivierende retinitis. Graefes Arch Clin Exp Ophthalmol 1866;12:211-5.
6. Lotery A, Sivaprasad S, O'Connell A, Harris RA, Culliford L, Ellis L, *et al.* Eplerenone for chronic central serous chorioretinopathy in patients with active, previously untreated disease for more than 4 months (VICI): A randomised, double-blind, placebo-controlled trial. Lancet 2020;395:294-303.
7. Fraenkel D, Suffo S, Langenbucher A, Seitz B, Abdin AD. Eplerenone for treatment of chronic central serous chorioretinopathy. Eur J Ophthalmol 2021;31:1885-91.
8. Zucchiatti I, Sacconi R, Parravano MC, Costanzo E, Querques L, Montorio D, *et al.* Eplerenone versus observation in the treatment of acute central serous chorioretinopathy: A retrospective controlled study. Ophthalmol Ther 2018;7:109-18.
9. Moein HR, Bierman LW, Novais EA, Moreira-Neto C, Baumal CR, Rogers A, *et al.* Short-term eplerenone for treatment of chronic central serous chorioretinopathy; a prospective study. Int J Retina Vitreous 2019;5:39.
10. Schwartz R, Habot-Wilner Z, Martinez MR, Nutman A, Goldenberg D, Cohen S, *et al.* Eplerenone for chronic central serous chorioretinopathy-a randomized controlled prospective study. Acta Ophthalmol 2017;95:e610-8.
11. Bousquet E, Beydoun T, Zhao M, Hassan L, Offret O, Behar-Cohen F. Mineralocorticoid receptor antagonism in the treatment of chronic central serous chorioretinopathy: A pilot study. Retina 2013;33:2096-102.
12. Bousquet E, Dhundass M, Lejoyeux R, Shinojima A, Krivosic V, Mrejen S, *et al.* Predictive factors of response to mineralocorticoid receptor antagonists in nonresolving central serous chorioretinopathy. Am J Ophthalmol 2019;198:80-7.
13. Cakir B, Fischer F, Ehlken C, Bühler A, Stahl A, Schlunck G, *et al.* Clinical experience with eplerenone to treat chronic central serous chorioretinopathy. Graefes Arch Clin Exp Ophthalmol 2016;254:2151-7.
14. Gergely R, Kovács I, Schneider M, Resch M, Papp A, Récsán Z, *et al.* Mineralocorticoid receptor antagonist treatment in bilateral chronic central serous chorioretinopathy: A comparative study of exudative and nonexudative fellow eyes. Retina 2017;37:1084-91.
15. Ghadiali Q, Jung JJ, Yu S, Patel SN, Yannuzzi LA. Central serous chorioretinopathy treated with mineralocorticoid antagonists: A one-year pilot study. Retina 2016;36:611-8.
16. Singh RP, Sears JE, Bedi R, Schachat AP, Ehlers JP, Kaiser PK. Oral eplerenone for the management of chronic central serous chorioretinopathy. Int J Ophthalmol 2015;8:310-4.
17. Toto L, D'Aloisio R, Mastropasqua R, Di Antonio L, Di Nicola M, Di Martino G, *et al.* Anatomical and functional changes of the retina and the choroid after resolved chronic CSCR. J Clin Med 2019;8:474.
18. Borrelli E, Zuccaro B, Zucchiatti I, Parravano M, Querques L, Costanzo E, *et al.* Optical coherence tomography parameters as predictors of treatment response to eplerenone in central serous chorioretinopathy. J Clin Med 2019;8:1271.
19. Karagiannis D, Parikakis E, Kontomichos L, Batsos G, Chatziralli I. The effect of eplerenone in chronic central serous chorioretinopathy refractory to photodynamic therapy. Semin Ophthalmol 2019;34:436-41.
20. Leisser C, Hirnschall N, Hackl C, Plasenzotti P, Findl O. Eplerenone in patients with chronic recurring central serous chorioretinopathy. Eur J Ophthalmol 2016;26:479-84.
21. Venkatesh R, Pereira A, Jayadev C, Prabhu V, Aseem A, Jain K, *et al.* Oral eplerenone versus observation in the management of acute central serous chorioretinopathy: A prospective, randomized comparative study. Pharmaceuticals (Basel) 2020;13:170.
22. Petkovsek DS, Cherfan DG, Conti FF, Hom GL, Ehlers JP, Babiuch AS, *et al.* Eplerenone for the treatment of chronic central serous chorioretinopathy: 3-year clinical experience. Br J Ophthalmol 2020;104:182-7.
23. Sampo M, Soler V, Gascon P, Ho Wang Yin G, Hoffart L, Denis D, *et al.* Eplerenone treatment in chronic central serous chorioretinopathy. J Fr Ophtalmol 2016;39:535-42.
24. Toto L, Ruggeri ML, Evangelista F, Viggiano P, D'Aloisio R, De Nicola C, *et al.* Choroidal modifications assessed by means of choroidal vascularity index after oral eplerenone treatment in chronic central serous chorioretinopathy. Eye (Lond) 2023;37:1214-8.
25. Rahimy E, Pitcher JD 3rd, Hsu J, Adam MK, Shahlaee A, Samara WA, *et al.* A randomized double-blind placebo-control pilot study of eplerenone for the treatment of central serous chorioretinopathy (ECSELSIOR). Retina 2018;38:962-9.
26. Chin EK, Almeida DR, Roybal CN, Niles PI, Gehrs KM, Sohn EH, *et al.* Oral mineralocorticoid antagonists for recalcitrant central serous chorioretinopathy. Clin Ophthalmol 2015;9:1449-56.