·Clinical Research·

Oral eplerenone for the management of chronic central serous chorioretinopathy

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Abstract

• AIM: To examine eplerenone (Inspra, Pfizer), a mineralocorticoid receptor antagonist, as a treatment option for chronic central serous chorioretinopathy (CSCR).

• METHODS: A retrospective consecutive case series was conducted for patients receiving oral eplerenone for chronic CSCR. At baseline and each follow-up visit, spectral domain optical coherence tomography (SD-OCT) imaging was performed, including manual measurements of the height and diameter size of subretinal fluid. The primary outcome measure was the reduction in subretinal fluid following initiation of therapy.

• RESULTS: A total of 17 eyes of 13 patients treated with 25 and 50 mg of oral eplerenone per day were identified. Subretinal fluid (SRF) decreased over time following eplerenone therapy (P= 0.007 and P=0.002, diameter and height respectively). Maximum SRF height decreased from a mean of 131.5 μm at baseline to 15.3 μm at day 181+. SRF diameter decreased from an average of 2174.4 μm at baseline to 46.9 μm at day 181+. LogMAR visual acuity improved from 0.42 (Snellen equivalent: 20/53) at baseline to 0.29 (Snellen equivalent: 20/39) at day 181+ (P= 0.024). Central subfield thickness (CST) decreased from 339.5 μm at baseline to 270.3 μm at day 181+ (P= 0.029).

• CONCLUSION: Eplerenone therapy resulted in significant anatomic and visual improvements in eyes with chronic CSCR.

• **KEYWORDS:** central serous chorioretinopathy; central serous retinopathy; central serous chorioretinopathy; eplerenone; subretinal fluid

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INTRODUCTION

Chronic central serous chorioretinopathy (CSCR) is a vision-threatening disease characterized by serous subretinal fluid (SRF) accumulation causing a localized area of retinal detachment [1-3]. The disruption of the outer retinal barrier leads to the accumulation of SRF [4]. CSCR affects about 1 in 10 000 people, with men affected more commonly than women[1-3]. Current treatment options include focal laser photocoagulation, photodynamic therapy (PDT) with verteporfin, anti-vascular endothelial growth factor (anti-VEGF) agents, corticosteroid inhibition, and adrenergic receptor inhibition [1-5]. None of these treatments have been studied in a large prospective clinical trial and these treatment modalities have variable outcomes.

CSCR exhibits a pathogenesis that is complex and not fully understood. Gass [6] indicates that the disease may start in the choroidal blood vessels. The observation of fibrin in the subretinal space indicates the presence of focal areas of increased capillary permeability of the choriocapillaries in patients with CSCR. This has been supported by findings with indocyanine-green angiography which show subretinal leakage of dye representing choroidal vascular hyperpermeability [7-9]. In addition, it has been proposed that excessive glucocorticoid-dependent choroidal mineralcorticoid receptor (MR) activation in choroid vessels may be involved in the pathogenesis of CSCR [1,2,4]. This is supported by the fact that CSCR has been proven to become more aggravated by endogenous or exogenous glucocorticoids[1-5]. Zhao *et al* [4] observed this trend when rat choroid was thickened after the introduction of a high dose of glucocorticoids, specifically resulting from binding to MR. MR are expressed in neuroretina and excessive activation of MR may promote retinal neovascularization [1]. Animal models and case reports have demonstrated that aldosterone-induced thickening was inhibited by the presence of an MR antagonist[1-4].

Therefore, the use of MR drugs such as oral eplerenone has been considered as a treatment option for patients with CSCR. Eplerenone acts as a competitive antagonist with excellent selectivity of the MR[10]. A pilot study of 13 patients conducted by Bousquet *et al* [2] demonstrated encouraging results of significant decreases in central macular thickness and subretinal fluid along with significant improvement in

visual acuity. Unfortunately, the current literature lacks a larger case series of patients on oral eplerenone with chronic CSCR, and there is a great need to observe and assess the efficacy of this treatment option.

SUBJECTS AND METHODS

After Cleveland Clinic Institutional Review Board (IRB) approval, a retrospective analysis was conducted for patients who received off-label oral eplerenone for treatment of chronic CSCR. The study adhered to the tenets of the Declaration of Helsinki. Chronic CSCR was defined as patients who exhibited the angiographic findings of CSCR with the presence of subretinal fluid for greater than 4mo without improvement similar to what was used by Bousquet *et al* [2]. This definition was chosen since CSCR is a fluctuating and spontaneously regressing disease especially in its acute stage and therefore only chronic, non-improving cases were selected for treatment.

Key inclusion criteria included patients on 25 or 50 mg/d of eplerenone for chronic CSCR. Key exclusion criteria included subjects who had a history of retinal vascular diseases including diabetic retinopathy, previous retinal vein occlusion affecting the retina, diabetic macular edema, exudative age-related macular degeneration, or a history of uveitis within the study eye.

The approved labeled use for eplerenone is for adult hypertension at a dosage of 50 mg orally once a day [11]. General side effects include flu-like symptoms and fatigue. Metabolic side effects include hyperkalemia (>5.5 mEq/L), hypercholesterolemia, and hypertriglyceridemia. Nervous system side effects include dizziness and headaches. Renal side effects include albuminuria and respiratory side effects include coughing. Gastrointestinal side effects include abdominal pain and diarrhea. Endocrine side effects in males include gynecomastia and mastodynia. Female patients may exhibit vaginal bleeding. Hepatic side effects include increase in serum alanine aminotransferase (ALT) and gamma glutamyl transpeptidase (GGT).

Eye examination findings including best correct Snellen visual acuity (converted to logMAR visual acuity for analysis) and imaging results by optical coherence tomography (OCT) were collected for analysis. The primary outcome measure was the reduction in subretinal fluid diameter and height at 90d following initiation of therapy. Secondary outcome measures included logMAR visual acuity, central subfield thickness, cube volume, and cube average retinal thickness.

Statistical Methods Because of the retrospective nature of the study, the follow up time periods were divided into 4 frames following initiation of therapy: baseline, 1-90d, 91-181d, and more than 181d. For some subjects which had more than one record in one time frame, for example, 29 and 71d in the 1-90 time frame, we predicted the outcome values at the middle of each time frame (45 in 0-90, 136 in 91-181, and 240 in 181+), assuming that the change in outcomes from visit to visit followed a linear trend.

Mixed models were used to assess the effect of time within subjects and to test the trends of outcomes over time. The time effect reports the trend amongst the four time frames evaluated. When the overall effect was significant, we used pairwise comparisons with a Bonferroni correction to specify which time parts differed. The test of trend was to assess whether the outcome changed over time following a consistent trend, defined by evaluating the means of each time frame. Least square means were adjusted means used to estimate overall effects in each time period while accounting for correlation between observations from the same subjects.

In the analysis of overall time effect and test of trend, height of SRF, diameter of SRF, and central subfield thickness (CST) were log-transformed before analysis, to satisfy the assumption of normality in mixed model. To compare each time frame with baseline, percentage change was used as the ratio of measurements at follow-up relative to baseline values. Outcomes were log-transformed for analysis, and transformed back for presentation. SAS version 9.3 (The SAS Institute Cary, NC, USA) was used to perform all analyses.

Imaging Protocol At baseline and each follow up visit, an spectral domain OCT (SD-OCT) macular cube and horizontal and vertical 5 raster scan protocols were performed with a Zeiss Cirrus HD-OCT (Cirrus version 6.1 software). SD-OCT measurements included the central subfield thickness (ILM-RPE), measurement of the height and diameter size of subretinal fluid using reading software, cube average thickness (average retinal thickness across the entire cube scan), and cube volume measurement.

RESULTS

Baseline Characteristics A cohort of 17 eyes in 13 patients with a history of chronic CSCR on eplerenone at the Cole Eye Institute was identified. Patients were treated for chronic CSCR with eplerenone (25 or 50 mg/d) for an average of 181d, ranging from 38 to 300d. The average patient age was 57, ranging from 29 to 85y and the average baseline visual acuity was 0.42±0.08 (Snellen equivalent: 20/53, ranging from 20/20 to 20/250). The average baseline CST (μm) was 339.5 (range: 211 to 874) and the baseline cube average thickness (μm) was 312.2, ranging from 226 to 527. The average cube volume (mm^3) at baseline was 11.2 (range: 8.1 to 18.8). Average baseline horizontal diameter SRF measurement (μm) was 2174.4 (range: 455 to 5520). Average baseline height SRF measurement (μm) was 131.5 (range: 43 to 706). These patients were previously treated with varying modalities. One patient had intravitreal triamcinolone (Triescence, Alcon) injection, one patient had PDT, two eyes of one patient underwent laser photocoagulation, six eyes received bevacizumab (Avastin, Genentech) injections, and two eyes received ranibizumab (Lucentis, Genentech) injections.

Study Outcomes Follow up time was cut into several frames and plotted using a mixed model analysis. Since time on eplerenone ranged from 38 to 300d, 3mo divisions were chosen as a time frame to avoid multiple visits in one period for each observation; thus, breaking time into baseline visit, 1-90d, 91-181d, and 181+d. There were only 8 observations between 180-300d, so it was not reasonable to divide this time segment into smaller sections. The retrospective nature of this study allowed for limited follow-up visits; however, there were no patients who dropped from the study. One patient with two eyes enrolled in the study was being treated for nonfoveal SRF and was removed from the SRF analyses.

At study completion, average logMAR was 0.29 (range 0.12-0.46; Figure 1) (Snellen equivalent of 20/39, ranging from 20/20 to 20/200). Average CST at study completion was 270.3 μm (range: 219.2-333.2 μm; Figure 2). Average cube volume (mm^3) was 10.2 (range 8.9-11.5-mm^3) and cube average thickness was 281.9 μm (range: 245.2-318.6 μm). Average horizontal SRF diameter measurement was 15.3 μm (range: 4.0-59.1 μm; Figure 3) and average SRF height measurement was 46.9 μm (range: 6.8-321.2 μm; Figure 4).

Central subfield thickness at the first follow-up significantly decreased 10% from baseline (P=0.048). LogMAR, CST, horizontal SRF diameter, and vertical SRF height had statistically significant decreases at the third follow-up compared with baseline (P= 0.024, P= 0.023, P= 0.002, and P= 0.007, respectively). Cube volume and cube average thickness did not have statistically significant decreases from baseline at any follow-up dates (P> 0.05).

Six eyes (35.3%) within the study demonstrated complete resolution of SRF at treatment completion, which ranged from 90 to 181+d as time of resolution. Eight eyes (47.1%) demonstrated no treatment effect throughout treatment duration. Two eyes (11.8%) improved but had incomplete resolution after treatment, while one eye (5.9%) exhibited worsened SRF on OCT. Figure 5 demonstrates a representative case treated with eplerenone.

Safety Analysis Safety was assessed through collection and summary of ocular and nonocular adverse events (AEs), systemic adverse events (SAEs), and ocular assessments as detailed in the patients medical record. There were no serious events that occurred as a result of eplerenone treatment.

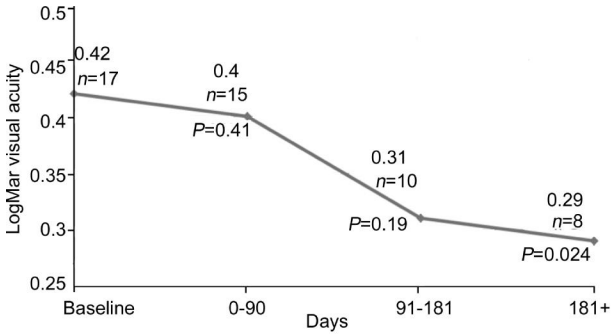

Figure 1 Average logMar visual acuity.

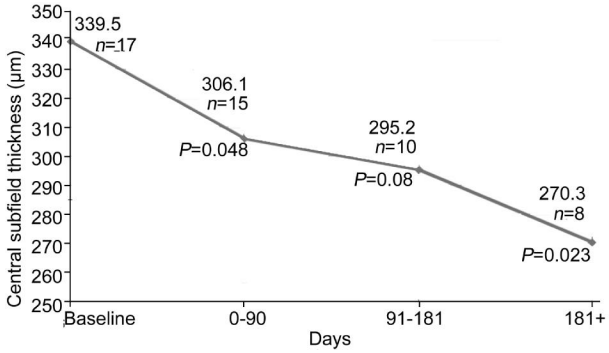

Figure 2 Average central subfield thickness.

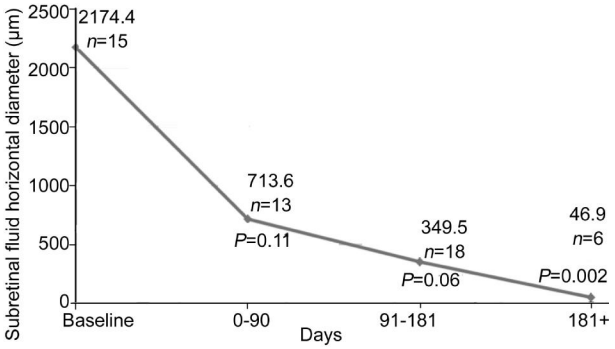

Figure 3 Average horizontal diameter subretinal fluid measurements.

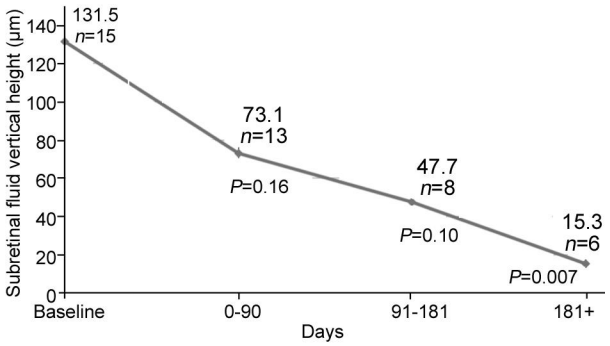

Figure 4 Average vertical diameter subretinal fluid measurements.

DISCUSSION

This series of patients treated with oral eplerenone 25 mg or 50 mg per day for chronic CSCR demonstrated statistically significant reductions in both horizontal and vertical subretinal fluid measurements as well as reduced central subfield thickness along with improved visual acuity. Central subfield thickness at the first follow-up period significantly decreased 10% from baseline (P= 0.048). LogMAR, CST, horizontal SRF diameter, and vertical SRF height had statistically significant decreases at the third follow-up compared with baseline (P= 0.024, P= 0.023, P= 0.002, and P= 0.007, respectively). Cube volume and cube average thickness did not exhibit significant decreases from baseline at any follow-up visits (P> 0.05).

The results of this study suggest that oral eplerenone may be effective in the treatment of CSCR, and should be investigated as a potential treatment choice in chronic cases.

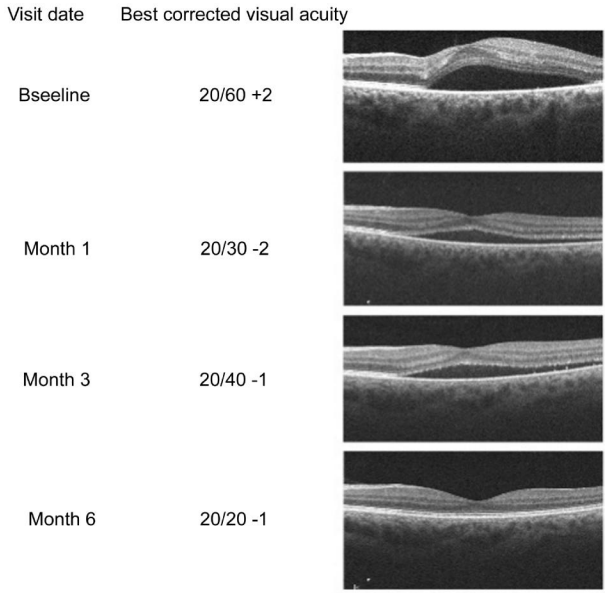

Figure 5 Representative patient on eplerenone demonstrating treatment response.

Given the high incidence of bilateral CSCR, oral eplerenone may be more beneficial than previous CSCR treatment modalities such as focal laser photocoagulation or PDT, as it is a treatment that targets the entire retina versus specific areas [2,5,12]. Additionally, laser photocoagulation treatment was not shown to reduce the incidence of recurrent or chronic CSCR and is more effective in acute CSCR [13]. Oral eplerenone is also less invasive than laser treatment and anti-VEGF injections. Given the small sample size of this study as well as the lack of a placebo-controlled group, more clinical studies are warranted to validate these findings.

One of the difficulties in determining treatment efficacy of an agent in CSCR is that the course is one of relapses and remissions. Any cases of acute CSCR, which typically have a better prognosis, were not treated with eplerenone. Ideally, a controlled chronic CSCR cohort would be helpful when comparing the efficacy, but this would require a prospective randomized clinical trial or a very large sample size to discern a difference. Instead, it might have been possible to include patients as controls of themselves (pre- and post-treatment changes). When examining this cohort data prior to eplerenone treatment, there were a number of patients who were treated with eplerenone immediately at first encounter date, with knowledge that the patient had chronic CSCR with notes from other physicians. Also, these same patients have limited OCTs prior to eplerenone treatment. These patients could have been excluded from the control group, but then the study loses significant power when determining the efficacy of the investigational treatment.

One difference of the present study in comparison to the initial study by Bosquet *et al* [2] was the variability in eplerenone dosing. Within this study, physicians prescribed 25 mg/d or 50 mg/d of oral eplerenone after disease confirmation. Four of the thirteen patients began treatment on oral eplerenone 25 mg/d, and were switched to 50 mg/d in the middle of the study. Six of the thirteen patients began and continued treatment on oral eplerenone with 50 mg/d, while the remaining 3 patients began and continued treatment on oral eplerenone with 25 mg/d. In Bousquet *et al*[2] case series, all 13 patients were treated with 25 mg/d for a week followed by 50 mg/d for 1 or 3mo. Despite the difference in dosing, this study noted significant decreases in central macular thickness, subretinal fluid, and BCVA. Case reports published by Zhao *et al* [4] used the same dosing scheme as Bousquet *et al* [2] and found similar significant results. In fact, they noted no recurrence of CSCR symptoms up to 5mo after discontinuation of drug treatment. Therefore it appears that the optimal dose and duration of eplerenone treatment for chronic CSCR need to be studied further.

It is important to note that this study lacked a definite record of the initial diagnosis date, as physicians at this study site commonly receive patient consults from outside physicians thus possibly creating referral bias in this cohort. However, these patients were placed on eplerenone treatment with confirmation from the referring physician notes that the patient presents chronic CSCR. Fluorescein leakage was not assessed in this study before and after treatment, despite fluorescein angiographs having been performed to confirm the disease prior to enrollment. Additionally, because of the small sample size and retrospective nature of the study, we could not confirm if the benefits of eplerenone treatment were sustained over a longer period of time in all patients or if SRF returned after discontinuation of eplerenone treatment. In addition, only 6-8 eyes completed 181+d, and therefore an ongoing study is planned to evaluate the long term anatomic and visual outcomes following treatment.

The purpose of this study was to examine eplerenone, a mineralocorticoid receptor antagonist, as a treatment option for chronic CSCR. The goal of eplerenone treatment for chronic CSCR was to reduce and resolve foveal SRF while improving visual outcomes. Following therapy, there was a significant reduction in subretinal fluid, reduction in CST, and improved visual acuity in eyes with chronic CSCR. A majority of eyes (47.1%) demonstrated stable SRF on treatment, while 35.3% had complete resolution of SRF. Results of this study indicate that eplerenone could be beneficial in the treatment of unresolved CSCR. The variability in eplerenone dosing within this study in comparison to past case reports, while demonstrating similar significant results, highlights the necessity for larger prospective trials to investigate the dosing and treatment paradigm of eplerenone for chronic CSCR.

ACKNOWLEDGEMENTS

Conflicts of Interest: Singh RP, None; **Sears JE,** None; **Bedi R,** None; **Schachat AP,** None; **Ehlers JP,** None; **Kaiser PK,** None.

REFERENCES

1 Gruszka A. Potential involvement of mineralcorticoid receptor activation in the pathogenesis of central serous chorioretinopathy: a case report. *European Review for Medical and Pharmacological Sciences.* 2013;17: 1369-1373

2 Bousquet E, Beydoun T, Zhao M, Hassan L, Offret O, Cohen-Behar F. Mineralcorticoid receptor antagonism in the treatment of chronic central serous chorioretinopathy: a pilot study. *Retina* 2013;33(10):2096-2102

3 Bouzas EA, Karadimas P, Pournaras CJ. Central serous chorioretinopathy and glucocorticoids. *Surv Ophthalmol* 2002;47(5):431-448

4 Zhao M, Celerier I, Bousquet E, Jeanny JC, Jonet L, Savoldelli M, Offret O, Curan A, Farman N, Jaisser F, Behar-Cohen F. Mineralcorticoid receptor is involved in rat and human ocular chorioretinopathy. *J Clin Invest* 2012;122(7):2672-2679

5 Quin G, Liew G, Ho IV, Gillies M, Fraser-Bell S. Diagnosis and interventions for central serous chorioretinopathy: review and update. *Clin Experiment Ophthalmol* 2013;41:187-200

6 Gass JDM. *Stereoscopic atlas of macular diseases: diagnosis and treatment*. 4th ed. St Louis: Moby Inc., 1997:52-70

7 Guyer DR, Yannuzzi LA, Slakter JS, Sorenson JA, Ho A, Orlock D. Digital indocyanine green videoangiography of central serous chorioretinopathy. *Arch Ophthalmol* 1994;112(8):1057-1062

8 Hayashi K, Hasegawa Y, Tokoro T. Indocyanine green angiography of central serous chorioretinopathy. *Int Ophthalmol* 1986;9(1):37-41

9 Piccolino FC, Borgia L. Central serous chorioretinopathy and indocyanine green angiography. *Retina* 1994;14(3):231-242

10 Delyani JA. Mineralcorticoid receptor antagonists: the evolution of utility and pharmacology. *Kidney Int* 2000;57(4):1408-1411

11 Drugs.com [Internet]. Eplerenone Information from Drugs.com; c2000-15. www.drugs.com/mtm/eplerenone.html

12 Lim JI, Glassman AR, Aiello LP, Chakravarthy U, Flaxel CJ, Spaide RF; Macula Society CSC Collaborative Study Group, Research and Education Committee and Website Committee. Collaborative retrospective macula society study of photodynamic therapy for chronic central serous chorioretinopathy. *Ophthalmology* 2014;121(5):1073-1078

13 Gemenetzi M, De Salvo G, Lotery AJ. Central serous chorioretinopathy: an update on pathogenesis and treatment. *Eye (Lond)* 2010;24 (12): 1743-1756

Retraction Notice

Retraction: "Which lamp will be optimum to eye? Incandescent, fluorescent or LED *etc* " by Liang Chen and Xiao-Wei Zhang published on *International Journal of Ophthalmology* 2014;7(1):163-168.

Authors of the above article failed to declare conflicts of interest, which violates the research ethics and moral norms. After a thorough investigation, we regret to announce that we must retract this article.

We regret any adverse effects this article may have caused.

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