

Eplerenone for Central Serous Chorioretinopathy: A Pilot Study

Protocol

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Part I

Aim and Hypotheses:

We would like to examine the short-term effects and safety of a systemic anti-aldosterone medication, eplerenone, in a small group of patients with central serous chorioretinopathy (CSCR), an idiopathic eye disease which affects the central vision and is known to be worsened or potentiated by elevated systemic corticosteroid levels.

In rat eyes, mineralocorticoid challenges have been shown to cause similar changes in the retina and choroid (choroidal vessel vasodilation, focal leakage, and increased choroidal thickness) as found in human patients with CSCR, suggesting that mineralocorticoids may play a role in potentiating CSCR.[1] Eplerenone, a mineralocorticoid receptor antagonist, has been shown to be of visual and anatomic benefit in a small retrospective series of 4 patients with chronic CSCR, suggesting that decreasing mineralocorticoid action in the eye may improve signs and symptoms of CSCR.[1] This data is enticing, and is the only current published evidence that eplerenone may be used to treat CSCR. However, in their study, the investigators only evaluated patients with chronic CSCR, and did so in a retrospective and uncontrolled fashion in only 4 patients.[1]

Our aim is to evaluate a standardized dose of eplerenone in a controlled prospective fashion for both acute and chronic CSCR. We hypothesize that aldosterone inhibition with eplerenone will decrease choroidal vessel vasodilation, focal leakage, and choroidal thickness in patients with both acute and chronic CSCR, leading to resolution of subretinal fluid and ultimately an improvement in symptoms. Sub-retinal fluid can be precisely measured using optical coherence tomography (OCT), an imaging technique discussed below.

Background:

Epidemiology of CSCR

Central Serous Chorioretinopathy (CSCR) is a disease of the choroid and retina that causes subretinal fluid to accumulate in the macula, the central and most important part of the retina.[2] CSCR is the fourth most commonly observed disease in a typical clinical practice of retinal disorders, after macular degeneration, diabetic retinopathy, and retinal vein occlusion, and affects 1 in 10,000 individuals over their lifetime.[3] Because of the involvement of the macula, CSCR causes distortion and blurring of

central vision.[2] It is most commonly idiopathic in nature, although CSCR has been associated with both exogenous (e.g., anabolic or prescribed corticosteroids, intra-articular corticosteroid injections, inhaled corticosteroids) and endogenous (e.g., Cushing's disease, etc.) increases in serum corticosteroid levels.[4] Systemic hypertension has also been associated with CSCR.[5] CSCR has been associated with high stress, and is more common in men.[2,6] CSCR typically affects people of middle-age, although it can occur in patients younger than 20 and older than 60 as well.[7] In the U.S., the disease is more common in Asian and Caucasian populations than in other racial groups.[8]

Prognosis of CSCR

There are two forms of the disease, acute CSCR and chronic CSCR.[8] In the acute phase, there is rapid accumulation of subretinal fluid in the macula. The fluid is then resorbed spontaneously, typically over 6-12 weeks.[8-11] Importantly for our study, only about 20% of patients with acute CSCR have complete resolution of fluid on OCT by 1 month. This was shown in randomized studies by Chan et al (4 of 19 patients) and Ratanasukon et al (6 of 29 patients).[12,13] Another study of 20 patients with acute CSCR showed the mean time to complete resolution of subretinal fluid on OCT was 65 days (range, 28–155).[14] In our clinical experience at Tufts, 10% or less of patients have complete resolution of subretinal fluid on OCT by 1 month after presentation.

Of note, even after fluid resorption, visual changes may still be reported by patients for several months after the initial episode.[15] The definition of chronic CSCR has not been agreed upon, but most of the literature defines it as sub-retinal fluid lasting more than 3 months, or recurrence of the disease within 1 year.[8-12] Chronic CSCR is also more likely to be bilateral, while acute CSCR more typically affects one eye at a time. Approximately 30-50% of all CSCR patients have recurrences of the disease, either in the same eye, opposite eye, or both eyes.[8,12] Patients with chronic CSCR can also develop intra-retinal fluid in addition to sub-retinal fluid.

Pathophysiology of CSCR

The pathophysiology of CSCR remains unclear, but recent studies using specialized imaging techniques have been helpful. CSCR is thought to be caused by an underlying abnormality in vascular permeability in the choroidal vessels, leading to elevation of the retinal pigment epithelium (RPE) from Bruch's membrane. The separated RPE may then undergo tiny rips, leading to direct connection between the choroid and the subretinal space. The RPE pump, which usually prevents accumulation of fluid under the retina, then dysfunctions or is overwhelmed, leading to build-up of serous fluid under the retina, the typical and characteristic feature of CSCR.[8,12] The abnormality in choroidal circulation is often bilateral. A familial predisposition is occasionally observed, although no clearly-defined pattern of inheritance has been elucidated.

Imaging in CSCR

Specialized imaging techniques are typically used to diagnose and follow patients with CSCR. Fluorescein angiography (FA) is the gold standard to diagnose the disease. The most characteristic finding is an expanding point of fluorescein leakage under the neurosensory detachment of the macula, seen in approximately 90% of patients.[8] Multiple points of leakage can be seen in some patients, particularly in chronic CSCR.[16] FA can be used to direct focal laser photocoagulation treatment or photodynamic therapy (both discussed below).

Optical coherence tomography (OCT) is also useful in diagnosing CSCR, and can be very helpful in monitoring disease activity over time. OCT takes images of the macula in cross-section with very high resolution (~5 um), allowing precise visualization and quantification of retinal thickness and amount of subretinal fluid over time. OCT can also demonstrate focal RPE detachments in patients with CSCR, in both affected and unaffected eyes.[17,18] Special OCT imaging protocols, called Enhanced Depth Imaging (EDI), allow improved visualization of choroidal thickness, which has been shown to be significantly thicker in patients with CSCR than in age-matched controls.[19] In patients with chronic CSCR, OCT can sometimes demonstrate intraretinal fluid in addition to subretinal fluid.

Other specialized imaging modalities, such as indocyanine green angiography (ICGA) and fundus autofluorescence, can also be used to help with the diagnosis.[8] Fundus autofluorescence detects subtle changes in the RPE, which can be affected in characteristic patterns in CSCR. ICGA highlights choroidal circulation, and can be particularly helpful for directing focal laser treatment or photodynamic therapy (both discussed below).

Treatment of CSCR

There have been few randomized trials looking at treatment of CSCR, and there is no gold standard for therapy. Without treatment, many patients have spontaneous resolution of fluid within three months of diagnosis. Focal laser photocoagulation has been used for treatment of some patients with acute CSCR. Studies suggest that this can hasten fluid resorption and decrease the rate of recurrence, but does not alter long-term visual prognosis.[20,21] Laser can only be used if there's a localized area of leakage on fluorescein angiography away from the center of the macula. Laser burns almost always leave a retinal scar and can result in a permanent scotoma. The scar can also lead to secondary formation of choroidal neovascularization. Therefore, focal laser is only advisable in select patients.[8]

Photodynamic therapy (PDT) is another type of laser treatment that was originally developed (and is FDA-approved) for neovascular age-related macular degeneration. PDT involves injecting a light-activated dye, verteporfin, intravenously, and then directing a "cold" laser to the region of interest in the retina. PDT offers a more directed treatment to the abnormal choroidal vessels, and can be targeted to the central macula as well as to multiple areas of leakage on fluorescein angiography. PDT has been used successfully in treating both acute and chronic CSCR.[12,22,23] In a randomized trial by Chan *et al* examining PDT for acute CSCR, 80% of patients (31 of 39) had complete resolution of fluid in the PDT arm one month after treatment, versus 20% of patients (4 of 19) in the control arm.[12] A number of trials have used PDT in

chronic CSCR, and the treatment seems to resolve fluid on OCT by one month in 50-100% of patients.[8,22-26]

However, PDT has a number of side effects, and it is not FDA-approved for the treatment of CSCR. Side effects include RPE changes, choriocapillary hypoperfusion, and choroidal neovascular membrane development, as well as severe skin reactions.[23] To decrease some of the ocular side effects, researchers have attempted to decrease the power of laser used; this is called “low-fluence” PDT. Small comparative studies suggest that low-fluence PDT is as effective as standard-fluence PDT, with fewer ocular side effects.[25,26] Most retina specialists now consider using low-fluence PDT for treatment of chronic CSCR.

A number of other small studies have shown possible benefits from a variety of systemic medications for acute and/or chronic CSCR, including steroid hormone antagonists (ketoconazole, mifepristone, eplerenone, finasteride),[1,27-29] adrenergic receptor antagonists (metoprolol, propranolol),[30,31] and carbonic anhydrase inhibitors (acetazolamide).[32] The most promising results seem to be with steroid hormone antagonists: finasteride, mifepristone, and eplerenone. Eplerenone is of particular interest, as this medication does not have as many anti-testosterone side effects as the other two agents.

Eplerenone for CSCR

Eplerenone is a selective aldosterone-receptor antagonist that was originally approved by the FDA in 2002 for the treatment of hypertension, and was subsequently approved in 2003 for patients with congestive heart failure (CHF) after myocardial infarction. Eplerenone is a derivative of spironolactone, a non-selective aldosterone-receptor antagonist, and has 1 to 2 times the potency of spironolactone. The most striking difference between the 2 drugs is in their affinity for androgen and progesterone receptors. Eplerenone has up to a 500-fold lower affinity for these receptors compared with spironolactone, which translates into a 3- to 10-fold decrease in progestogenic and antiandrogenic adverse effects.[33,34]

In the vasculature, increased aldosterone (mineralocorticoid) levels can lead to increased inflammation, increased vascular reactive oxygen species, and decreased nitric oxide production. These effects alter endothelial and smooth muscle in blood vessels, affecting the contractility properties of arteries, arterial tone, and blood pressure.[35] In the retina, mineralocorticoid levels may affect both the choroidal and retinal circulations. Zhao and colleagues recently demonstrated in rats that intravenous mineralocorticoid injection induced choroidal vessel dilation and leakage and increased choroidal thickness, findings that are similar to those found in patients with CSCR.[1] They postulated a potential benefit of mineralocorticoid inhibition in patients with CSCR.

Zhao and colleagues then described encouraging results of eplerenone treatment in four patients with chronic CSCR.[1] They gave two patients 25 mg of eplerenone daily for one week, followed by a higher dose of 50 mg daily for four weeks. The other two patients received 50 mg eplerenone for three months. All four patients demonstrated complete resolution of subretinal fluid on OCT. In addition, after five months of follow-up, none of the patients had a recurrence of fluid on OCT. Similar results in about twenty patients have been reported to us by Peter Kaiser of the Cole

Eye Institute at the Cleveland Clinic.[36] He has used 25 mg daily eplerenone in patients with chronic CSCR, and noted that most patients demonstrated a positive response by four weeks.

Eplerenone is a relatively safe medication, but it can lead to raised serum potassium levels (i.e., hyperkalemia), which can be potentially life-threatening. In a large clinical trial of patients with CHF, the incidence of serious hyperkalemia, defined as a serum potassium concentration ≥ 6 mEq/L, was 5.5% in the eplerenone group and 3.9% in the placebo group. Patients with a lower creatinine clearance at baseline had a higher incidence of serious hyperkalemia.[37]

Eplerenone comes in two doses, 25 mg and 50 mg. The standard dose for treatment of hypertension is 50 mg daily. For patients with an inadequate blood pressure response to 50 mg, the dosage is increased to 50 mg twice daily. For treatment of CHF, patients are started on 25 mg, and escalated to 50 mg within four weeks. Dose adjustment in CHF patients takes place based on serum potassium levels as follows: < 5.0 mEq/L – Increase to 50 mg once daily; 5.0 – 5.4 mEq/L – Maintain dose; 5.5 – 5.9 mEq/L – Decrease to 25 mg every other day; ≥ 6.0 mEq/L – Withhold and restart at 25 mg every other day when potassium levels fall to < 5.5 mEq/L.[38]

The other notable side effects with aldosterone-receptor antagonist medications are related to cross-reactivity with sex hormone receptors. Eplerenone has a much lower incidence of anti-sex hormone effects than spironolactone. With eplerenone, sex hormone-related events, such as breast enlargement in men, breast pain, or menstrual abnormalities, have been reported in up to 2.5% of patients, although some studies reported no such events.[39-41]

Because of the elevations in serum potassium concentrations and consequent increased risk for hyperkalemia with eplerenone, use of this drug is contraindicated in patients at increased risk for hyperkalemia, including those with a serum potassium concentration > 5.5 mEq/L, type 2 diabetes and microalbuminuria, a serum creatinine concentration > 2 mg/dL in men and > 1.8 mg/dL in women, or a creatinine clearance < 50 mL/min, and during concomitant administration of potassium supplements, potassium-sparing diuretics, and/or potent CYP3A4 inhibitors.[38] It is recommended to check serum potassium and creatinine before initiating eplerenone therapy, followed by serum potassium within the first week and at one month after the start of treatment.[38]

Part II

Experimental Protocol:

Study Design

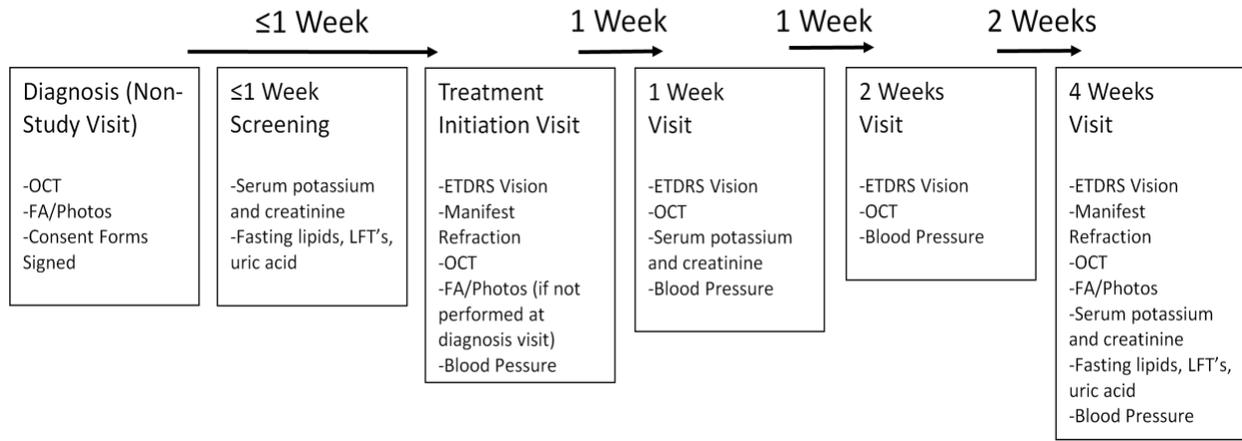
- Prospective, consecutive, non-randomized, non-blinded, non-comparative interventional pilot study
- Eligible patients will be those who present with CSCR, both acute and chronic types
- 20 patients will be enrolled; participation is voluntary and all interested patients must provide written informed consent to take part in the study

- Chronic CSCR will be defined as persistent subretinal fluid on OCT ≥ 3 months after initial presentation to the eye clinic, and $< 50\%$ reduction in fluid thickness on OCT after 3 months.
- Only one eye of a participant will be included in the study, although both eyes will be evaluated. In patients with bilateral CSCR, the worse eye will be the study eye.
- Patients will be evaluated and treated at the New England Eye Center (NEEC)
- All participants will receive a standard ophthalmic examination as well as color fundus photographs, fluorescein angiography, and macular OCT (see below for specific imaging protocol).
- Treatment will be the standard dose of eplerenone, 50 mg pills taken one pill daily over four weeks
- Subjects participation will include 4 visits to the NEEC:
 - o Treatment initiation
 - o 1 week after initiation
 - o 2 weeks after initiation
 - o 4 weeks after initiation
- Prior to initiating treatment, all subjects will have laboratory testing to confirm healthy ranges of the following lab tests will include: serum potassium, creatinine, electrolytes, liver function tests, uric acid, and fasting cholesterol.
- Serum potassium and creatinine levels will be re-tested at the 1 week visit.
- All lab tests will be repeated at the 4 week visit
- Blood pressure will be measured at each visit
- A database of enrolled participants will be maintained on a password protected desktop computer at the New England Eye Center.
- When the study is complete, all data will be de-identified and coded.

Study Assessments/Schematic

Study Protocol

-4 to 5 weeks total
 -20 patients with CSCR (Acute or Chronic)



Initial Diagnosis and Enrollment

1. In order to diagnose CSCR, patients typically undergo a routine ophthalmic examination, fundus photographs, fluorescein angiography, and OCT images. Patients may undergo fundus autofluorescence testing or indocyanine green angiography at the discretion of the physician to confirm the diagnosis of CSCR. These tests are done routinely in the eye clinic and are not included as part of the study protocol.
2. Once a potential participant with CSCR is identified, he or she will be invited to participate in this study. Participation is voluntary; potential participants may refuse to participate in this study and their medical care will not be affected in any way. Written informed consent will be obtained by one of the investigators, at the initial diagnosis visit. If the patients wish, they can consider whether or not to enroll in the study, and enroll at a later date if they so choose. If any non-English subjects are eligible for enrollment in the study, they will be enrolled using interpreters and IRB approved short forms as per the Tufts MC / TUHS IRB Short Form Policy. The investigator will discuss and explain the study to the potential participant. Special care will be taken to avoid the possibility of coercion in soliciting volunteers. Informed consent documents will be kept on file at the New England Eye Center. Strict confidentiality will be observed for participant record information required for documenting study results. The participants will be informed that the study adheres to the Health Insurance Portability and Accountability Act (HIPAA) and participants will have the opportunity to ask questions about the study. Understanding of the study will be assessed by the investigator or sub-investigator; the patient will be required to demonstrate a

clear appreciation and understanding of the facts, implications, and future consequences of being enrolled in the study.

3. Before enrollment, patients will be offered focal laser therapy and/or photodynamic therapy (PDT) if the physician feels this treatment may be warranted. Notably, there is no standard of care for either acute or chronic CSCR. It is unknown whether PDT may be more effective in treating CSCR if given sooner. In addition, prior authorization from medical insurance is needed for photodynamic therapy, and patients often have to wait a few weeks before PDT can be administered, therefore the process of prior authorization may be initiated concurrently to enrollment in this study if the physician feels PDT may be warranted after completion of the study.
4. *Screening Period:* Prior to starting eplerenone therapy, there will be a screening period (≤ 1 week) when serum potassium and creatinine will be evaluated. Patients will be excluded if they have a serum potassium concentration ≥ 5.0 mEq/L, a serum creatinine concentration > 2 mg/dL in men and > 1.8 mg/dL in women, or a creatinine clearance < 50 mL/min, or during concomitant administration of potassium supplements, potassium-sparing diuretics, and/or potent CYP3A4 inhibitors (see below under *Exclusion Criteria*). Additional serum tests of electrolytes, liver function tests, uric acid, and a fasting cholesterol panel will be obtained before initiating therapy. Although there are no exclusion criteria based on these additional laboratory tests, values will be compared to those after 1 month of therapy and abnormalities will be included in safety outcome evaluation at the end of the study. 7.5 to 10 ml of blood will be collected at this visit, as well as a urine sample.
5. Eplerenone is contraindicated in patients who have both type 2 diabetes and microalbuminuria. If a patient has type 2 diabetes, a urinalysis will be performed prior to starting treatment. Patients with type 2 diabetes and microalbuminuria will be excluded from the study.

Eplerenone is considered a pregnancy class B medication, which means that animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women, or that animal studies have shown an adverse effect, but that adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester. Women of child-bearing potential will be tested for pregnancy at during the initial screening testing, with a urine pregnancy test.

Study Visits

1. After the screening period, patients will come to the NEEC for the first official study visit, the "Treatment Initiation Visit", which includes specific vision screening, blood pressure measurement, and OCT imaging as per study protocol. Patients will be given a bottle containing 28 tablets of eplerenone 50mg, and will start eplerenone the same day. Medication will be provided by the Tufts Research

Pharmacy. Patients will then return to the clinic at 1 week, 2 weeks, and 4 weeks after baseline.

2. At baseline and all subsequent study visits, participants will be examined by an ophthalmologist at the NEEC using conventional techniques. The eye examination will include visual acuity testing using the ETDRS chart, extra-ocular motility, intraocular pressure measurement, and a routine slit lamp and dilated fundus examination. Manifest refraction will be performed at the baseline visit and at week 4. Pupils will be dilated with standard dilating drops given via one drop to both eyes one-half hour prior to eye examination).
3. *Visual Acuity*: Best-corrected visual acuity is a secondary endpoint in this study. Refraction and testing of visual acuity will be standardized using the ETDRS protocol. Certified refractionists and visual acuity examiners will be used. Examination lanes will utilize a starting distance of 4 meters according to the ETDRS protocol. Refraction will be performed at the baseline visit and at 4 weeks.
4. *Optical Coherence Tomography (OCT)*: OCT images will be acquired at each visit. The ophthalmic photographers will be responsible for explaining how the non-invasive OCT images are obtained, as occurs with all of our patients routinely. OCT will be obtained using a commercially available, FDA-approved system, the Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA). Both eyes will be scanned using an internal fixation point. The length of the test using Cirrus HD-OCT is approximately 5 minutes per eye. Scan protocols capturing 1 to 5 images with high image definition from a focal location can be used for qualitative assessment of the retinal structure. A denser scan pattern, the macular cube scan, captures 128 512-line images within a 6 mm x 6 mm area centered on the macula, allowing calculation of retinal thicknesses and volumes with high precision. Scan protocols include:
 - a. Cirrus HD-OCT 5 line raster scan
 - b. Cirrus HD-OCT single line scan
 - c. Cirrus HD-OCT 512x128 macular cube scan
 - d. Cirrus HD-OCT Enhanced Depth Imaging (EDI) scan
5. *Fluorescein Angiography*: Fluorescein angiography will be acquired at diagnosis and at 4 weeks after treatment initiation. Angiography will be explained to patients by either the physician or the ophthalmic nurse administering the intravenous dye. Patients routinely give verbal consent stating they understand the procedure and potential risks of fluorescein angiography. The procedure involved a special water-soluble dye (fluorescein) that is injected intravenously. As the dye passes through the blood vessels of the choroid and retina, the photographer takes a series of photographs in rapid succession, over a period of 5-10 minutes. The possible side effects of fluorescein angiography are discussed below.

Laboratory Testing: After initial screening, serum potassium and creatinine will be evaluated at 1 and 4 weeks after baseline. *See below for dosing adjustment instructions based on potassium levels.* Additional serum tests of electrolytes, liver function tests, uric acid, and a fasting cholesterol panel will be obtained before treatment and 4 weeks after baseline

Baseline and 4-week visits: Serum potassium, sodium, BUN, creatinine, glucose, chloride, total CO₂, calcium, AST, ALT, GGT, alkaline phosphatase, total and direct bilirubin, uric acid, albumin, total protein, fasting total cholesterol, fasting LDL, fasting LDL, fasting triglycerides. The initial and final blood draws will be roughly 7.5 to 10 ml of blood, or 2 teaspoons.

6. **1-week visit:** Serum potassium and serum creatinine. The 1-week blood draws will be roughly 4 ml of blood, or 1 teaspoon.

7. **Blood pressure:** Systolic and diastolic blood pressure will be recorded at all visits. Blood pressure will be measured in the seated position. When blood pressure is scheduled at the same time point as a blood sample draw, the blood pressure will be measured first.

8. The subject's participation in the research may be terminated by the principal investigator or co-investigator if there is any type of medical emergency or urgency that needs to be attended to first. If a subject decides to withdraw from the research, the patient will be offered routine ophthalmologic care at NEEC. If the patient prefers, he or she can be referred to an outside ophthalmologist for continued eye care. The subject's data and collected blood and urine samples will be discarded, although the reason for screen failure will be noted after the patient demographic data is de-identified.

Eligibility

Both male and female participants of any race will be enrolled.

Inclusion Criteria:

1. Age 18 or over
2. Ability to give written informed consent
3. Presence of sub-retinal fluid under the fovea as seen on OCT
4. Diagnosis of Acute or Chronic CSCR:
 - a. Acute CSCR: First presentation to eye clinic with visual symptoms, including decreased vision or visual distortion, and the characteristic appearance of CSCR on examination, fluorescein angiography, and OCT.
 - b. Chronic CSCR: Previous diagnosis of CSCR, persistent subretinal fluid on OCT \geq 3 months after initial presentation to the eye clinic, and <50%

reduction in fluid thickness on OCT after 3 months. *Patients who have had previous treatment for CSCR may be included.*

Exclusion Criteria:

1. Age less than 18
2. Persons with impaired decision-making ability.
3. Women who are known to be pregnant or are actively trying to conceive.
4. Additional eye disease affecting the macula or posterior retina.
5. At screening, serum potassium concentration ≥ 5.0 mEq/L, a serum creatinine concentration >2 mg/dL in men and >1.8 mg/dL in women, or a creatinine clearance <50 mL/min, and during concomitant administration of potassium supplements, potassium-sparing diuretics, and/or potent CYP3A4 inhibitors (amifostine, cyclosporine, fluconazole, itraconazole, ketoconazole, mifepristone, posaconazole, potassium salts, Rituximab, tacrolimus, voriconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, or nelfinavir).
6. Patients with type 2 diabetes will be screened for microalbuminuria with a urinalysis. If microalbuminuria is present, these patients will be excluded.

Data Elements

The data elements to be collected from each participant include age, gender, visual acuity, intraocular pressure, lens status, and retinal examination findings, color fundus photographs, fluorescein angiography images, and OCT images.

Primary Outcome

Presence or absence of subretinal fluid and/or intraretinal fluid on OCT after 4 weeks of treatment with 50 mg of eplerenone.

Secondary (Exploratory) Outcomes

- Change in central macular circle thickness on OCT, automatically calculated with OCT software after 1, 2, and 4 weeks of treatment
- Change in thickness of subretinal fluid under the fovea on OCT, manually calculated after 1, 2, and 4 weeks of treatment
- Change in thickness of choroid under the fovea on enhanced-depth imaging OCT, manually calculated, after 1, 2, and 4 weeks of treatment
- Change in best-corrected visual acuity before and after 4 weeks of treatment
- Change in dye leakage characteristics on fluorescein angiography before and after 4 weeks of treatment
- Change in the same OCT characteristics listed above, in the fellow eye
- Proportion of acute vs. chronic CSCR patients
- Safety and tolerability characteristics in this patient population via clinical laboratory data, blood pressure, and adverse events

Data Safety and Monitoring Plan

See below for details regarding monitoring of adverse events (AEs) and serious adverse events (SAEs). Data will be monitored with the patients' safety in mind. All adverse effects will be recorded by the Principal Investigator and Co-Investigators and will be reported to the IRB at the conclusion of the study. Should an SAE occur, it will be reported immediately to the Tufts MC / TUHS IRB by the Principal Investigator within 24 hours. The Principal Investigator and Co-Investigators will be responsible for collecting the patient data information. The information will then be de-identified and coded. The key to the code will only be accessed by the investigators.

Dose adjustment and/or stopping criteria

Serum potassium criteria

If serum potassium is ≥ 5.0 mEq/L and < 5.5 mEq/L at 1 week after initiation, dosing will be decreased to 25 mg every day and serum potassium will be rechecked at 1 week. If serum potassium is still ≥ 5.0 mEq/L and < 5.5 mEq/L after 1 additional week, dosing will be decreased to 25 mg every other day and serum potassium will be rechecked at 1 week. If serum potassium is still ≥ 5.0 mEq/L and < 5.5 mEq/L after 1 additional week, dosing will be withheld. If serum potassium is ≥ 5.5 mEq/L at 1 week, eplerenone will be withheld.

See below for definition of adverse events and serious adverse events.

Statistical Analysis

The primary outcome will be described by the proportion of patients without subretinal fluid on OCT at the end of the study period (see below for sample size and precision estimates). The 95% confidence interval (CI) for this proportion will also be estimated. Descriptive statistics are considered appropriate for this pilot study since there is currently no standard treatment for CSCR, and the data from this study may be used to design future, rigorous trials of eplerenone.

Changes in continuous secondary outcome measures will be described using mean, median, min/max, and standard deviations, and categorical secondary outcome measures will be described using frequencies and proportions.

Sample Size and Precision Calculations

The natural history of acute CSCR is to improve on its own. Studies have shown, however, that fluid resolution typically takes at least 6 weeks, and often takes as long as 3 months or longer. In a randomized study by Chan et al examining effects of half-dose photodynamic therapy in patients with acute CSCR, 20% of patients had complete resolution of fluid on OCT after 4 weeks, compared to 80% of patients treated with PDT.[12] Similar rates of complete fluid resolution have been reported after treatment with PDT, as well as in a small sample of patients with chronic CSCR treated with eplerenone.[1, 22-26] Based on these assumptions, a calculation was performed to determine the width of confidence intervals for the proportion of patients successfully

treated with eplerenone. If the treatment is effective for 70% of patients, a sample size of 10 patients will give a 95% confidence interval width of 0.586 that includes a lower bound of 0.348 (see range of widths with sample sizes of 10 and 15 below). The Research Design Center of the Clinical and Translational Sciences Institute at Tufts Medical Center assisted with these calculations.

Numeric Results for Two-Sided Confidence Intervals for One Proportion Confidence Interval Formula: Exact

Confidence Level	Sample Size (N)	Target Width	Actual Width	Proportion (P)	Lower Limit	Upper Limit	Width if P = 0.5
0.950	10		0.586	0.700	0.348	0.933	0.626
0.950	10		0.531	0.800	0.444	0.975	0.626
0.950	10		0.442	0.900	0.555	0.997	0.626
0.950	15		0.487	0.700	0.416	0.903	0.522
0.950	15		0.438	0.800	0.519	0.957	0.522
0.950	15		0.356	0.900	0.637	0.993	0.522

References

Flleiss, J. L., Levin, B., Paik, M.C. 2003. Statistical Methods for Rates and Proportions. Third Edition. John Wiley & Sons. New York.
 Newcombe, R. G. 1998. 'Two-Sided Confidence Intervals for the Single Proportion: Comparison of Seven Methods.' *Statistics in Medicine*, 17, pp. 857-872.

Safety Analysis

Safety data will be presented in tabular format and will be summarized descriptively.

PART III

1. How will participants be recruited?
 Participants will be recruited from the practices of the primary investigator and co-investigators.
2. Number of participants needed?
 The maximum number of participants over the entire study is expected to be 20.
3. Will participants receive any payment or other compensation for participation?
 No. There are no costs to subjects participating in this research study and he or she will not be billed for the visit. Eplerenone will be provided by the New England Eye Center.
4. Will participants be studied outside NEEC premises?
 No.

5. Will the facilities of the Clinical Research Center be used?
No.
6. Will drugs be used?
Yes. Eplerenone 50mg, an oral medication FDA-approved for use in systemic hypertension and congestive heart failure, will be used off-label for treatment of all patients in this study. Patients will be provided the medication by the investigational team. Funding is being provided by the Research Fund of the Ophthalmology Department at Tufts Medical Center.
7. Will radiation or radioactive materials be employed?
No.
8. Will special diets be used?
No.
9. Will participants experience physical pain or stress?
While some patients experience distorted vision as a result of CSCR, no additional physical distress to patients is expected as a result of this study.
10. Will a questionnaire be used?
No.
11. Are personal interviews involved?
No.
12. Will participants experience psychological stress?
No.
13. Does this study involve planned deception of participants?
No.
14. Can information acquired through this investigation adversely affect a participant's relationships with other individuals?
No.
15. Please explain how subjects' anonymity will be protected, and/or confidentiality of data will be preserved.
The data obtained from the study will be retained by Dr. Witkin and will be stored at NEEC for a minimum of 8 years per institutional policy. Members of the research study team including the principle and co-investigators will analyze the data. If results of this study are reported in medical journals or at meetings, subjects will not be identified by name, by

recognizable photograph, or by any other means. The subjects' medical records will be maintained according to the NEEC requirements.

Only the Primary investigators, Sub-investigators, and Clinical Research Coordinators will have access to research records. Electronic and paper data may place subject confidentiality at risk. To minimize or eliminate confidentiality risks, all study patients are communicated with in a private exam room, and all study data is coded and kept in locked file cabinets in the locked research room or on a password protected file on a computer which remains in the research room. All study charts are de-identified and all data inputted is de-identified. Research data, documents, reports, scans, and specimens, will only be shared amongst research team members. No data will be sent out of Tufts. Data will be recorded in study charts which are de-identified; no patient identifiers are listed on the chart. A numeric code will be assigned chronologically to each study patient. Research documents, files, and reports will be kept in the research office at the New England Eye center, on the 10th floor of the Biewend building. Files will be kept in the locked study file room in the eye department location at BD4. Screen failure data will not be retained.

PART IV

A. Please summarize the risks to the individual subject, and the benefits, if any:

Potential benefits:

In acute CSCR, the benefit of participating in the study relates to the hypothetical hastened resolution of subretinal fluid and an associated improvement in visual symptoms and visual acuity. In chronic CSCR, the benefit of participating in the study relates to the hypothetical resolution of subretinal and intraretinal fluid, and an associated improvement in visual symptoms and visual acuity.

Potential risks and discomforts:

Patients will be required to commit time for frequent visits to the eye clinic over the course of 4-5 weeks. There will be 3 separate blood sample draws. Ophthalmic imaging will be performed at each visit. Fluorescein angiography will be performed at initial diagnosis and at the final visit.

At each visit, patients may experience corneal irritation or drying. This irritation may result from staring at the light in the OCT machines. This side effect would be treated with artificial tears with essentially immediate relief. There may be minor discomfort caused by the light associated with the OCT imaging procedure. However, no pain or stress is expected as a result of the imaging. The light exposure for the OCT instruments is within documented safe limits set by the American National Standards Institute (ANSI). Since these measurements are being performed optically, there is no

contact required with the eye itself. All light exposures are kept within documented safe limits set by the American National Standards Institute (ANSI) for normal eyes.

The risks associated with the intraocular drops for dilating the eyes are minimal. These drops are used for all routine examinations by an ophthalmologist. The drops used to dilate the eye include tropicamide 1% and phenylephrine 2.5%. Side effects of tropicamide include an increase in the pressure of the eye, stinging, dryness of the mouth, blurred vision, increased sensitivity to light, increased heart rate, headache, or allergic reaction. Known side effects of phenylephrine include allergic reaction, irregular or fast heart rate, high blood pressure, burning, stinging, increased redness of the eye, tearing, blurred vision, headache, tremor, nausea, sweating, nervousness, dizziness, or drowsiness. Any of these symptoms would be managed according to standard protocol used in our office setting, as we use these drops on every patient undergoing a dilated eye examination.

Phenylephrine, one of the standard eye drops used for pupil dilation, is considered a pregnancy class C drug, which means that animal reproduction studies have shown an adverse effect on the fetus but that there are no adequate and well-controlled studies in humans. However, this eye drop is given routinely to patients in the office without a pregnancy test first, as well as to pregnant women who require a dilated eye examination, because the risk is felt to be minimal.

Fluorescein angiography will be performed at diagnosis and 4 weeks after initiation of treatment. Side effects will be discussed with each patient and verbal consent will be attained by treating physician and the photography department prior to performing this test for patients:

- Typically, after the fluorescein dye has been injected the patient's skin may appear yellow. This lasts for a period of several hours. This discoloration disappears once the dye has been filtered out of the bloodstream by the kidneys.
- Because the kidneys filter the dye from the bloodstream the patients' urine will be a very bright yellow-orange color for 24-36 hours.
- Approximately 20% of patients may experience nausea from the dye. This, however, usually passes within a minute.
- If the dye happens to leak out of the blood vessel at the time of injection, the patient may feel a burning sensation and may also notice a yellow discoloration of the skin. These symptoms pass on their own.
- Allergic reactions to fluorescein dye are rare. If they occur, they usually cause a skin rash and itching. This is usually treated with oral or injectable antihistamines, depending on the severity of the symptoms.
- Less common severe allergic reactions are cardiorespiratory reactions such as low blood pressure or shortness of breath (~1 in 4000 persons). Severe life-threatening allergic reactions are very uncommon (~1 in 200,000 persons).

Eplerenone is a potassium sparing diuretic, which is FDA approved to treat heart failure as well as high blood pressure, but is not FDA approved for treatment of central serous

chorioretinopathy. Eplerenone is considered a pregnancy class B medication, which means that animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women, or that animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester. The risks associated with the oral medication eplerenone are as follows:

Eplerenone 50mg

Serious side effects include:

- Increased serum potassium
- Increased serum cholesterol
- Abdominal or stomach pain
- Breast enlargement (men)
- Arm, back, or jaw pain
- Chest pain or discomfort
- Chest tightness or heaviness
- Confusion
- Difficulty with breathing
- Dizziness
- Fast or irregular heartbeat
- Headache
- Irregular heartbeat
- Large, hive-like swelling on the face, eyelids, lips, tongue, throat, hands, legs, feet, or sex organs
- Nausea
- Nervousness
- Numbness or tingling in the hands, feet, or lips
- Pain or discomfort in the arms, jaw, back, or neck
- Rash
- Shortness of breath
- Sweating
- Vomiting
- Weakness or heaviness of the legs

Less serious effects include:

- Abnormal vaginal bleeding
- Breast pain
- Chills
- Cloudy urine
- Cough
- Diarrhea
- Fever
- General feeling of discomfort or illness

- Joint pain
- Loss of appetite
- Muscle aches and pains
- Swelling of the breasts or breast soreness in both females and males
- Unusual tiredness or weakness

B. Detection and reporting of harmful effects:

The primary investigator and/or site staff will be responsible for detecting, documenting, and reporting events that meet the definition of an adverse event (AE) or serious adverse event (SAE).

AEs and SAEs will be collected from the time of informed consent into the study and until the last visit is completed. Medical occurrences that begin prior to the start of eplerenone but after obtaining informed consent may be recorded. Any unanticipated problems and AEs/SAEs will be reported as per the Tufts IRB's unanticipated problem and adverse event reporting policy.

Subjects will be told, verbally and in writing, that if they experience any post-procedure medical problems or have any questions, Dr. Witkin can be reached at (617) 636-7950 during the day or paged through the hospital operator after hours. If any medical problems occur in connection with this study, the NEEC will provide emergency care.

Definition of Adverse Events (AEs)

An AE is any untoward medical occurrence in a subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Events meeting the definition of an AE include:

- Any abnormal laboratory test results or vital sign measurements, including those that worsen from baseline, and felt to be clinically significant in the judgment of the investigator
- Exacerbation of a chronic or intermittent pre-existing condition
- New conditions detected or diagnosed after the drug initiation visit, even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction

Events that do not meet the definition of an AE include:

- Any clinically significant abnormal laboratory or vital sign findings that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition
- Progression of the disease being studied, unless more severe than expected for the subject's condition
- Anticipated day-to-day fluctuations of pre-existing diseases or conditions present or detected at the start of the study that do not worsen

Definition of Serious Adverse Events (SAEs)

If an event is not an AE as defined above, then it cannot be an SAE even if serious conditions are met. An SAE is any untoward medical occurrence that:

- Results in death
- Is life-threatening: An event in which the subject was at risk of death at the time of the event, not an event which might hypothetically have caused death if it was more severe
- Requires hospitalization: Hospitalization signifies that the subject was detained at the hospital for observation and/or treatment that would not have been appropriate in the outpatient setting. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in disability/incapacity: Substantial disruption of a person's ability to conduct normal life functions. This is not intended to represent minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma, which may interfere with everyday life but do not cause a substantial disruption.
- Results in a congenital anomaly/birth defect
- Is associated with elevation of serum potassium defined as a serum potassium level ≥ 6.0 mEq/L at any time-point after initiation of eplerenone therapy
- May jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed above

Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended questions are the preferred method to inquire about AE occurrence. Appropriate questions include:

- How are you feeling?
- Have you had any (other) medical problems since your last visit?
- Have you taken any new medications, other than eplerenone, since your last visit?

Recording of AEs and SAEs

When an AE/SAE occurs, it is the responsibility of the Primary Investigator to review all documentation relative to the event. The Primary Investigator will then record all relevant information regarding an AE/SAE. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. The investigator is obligated to assess the relationship between the investigational medication and the occurrence of each AE/SAE. The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with daily activities

- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities

An AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.

Reporting of SAEs

Any unanticipated problems and AEs/SAEs will be reported as per the Tufts IRB's unanticipated problem and adverse event reporting policy. If the investigator does not have all the information regarding the SAE, he/she will not wait to receive additional information before notifying the IRB of the event.

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