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Therapeutic Efficacy of Spironolactone for Central Serous Chorioretinopathy

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Purpose: To evaluate the therapeutic effects and safety of oral spironolactone (SPRL) in patients with central serous chorioretinopathy (CSC).

Materials and Methods: The medical records and imaging data of patients diagnosed with CSC and treated with SPRL were retrospectively reviewed. Central macular thickness (CMT), subretinal fluid (SRF) height, subfoveal choroidal thickness (SFCT), and best-corrected visual acuity (BCVA) at baseline, at 1, 3, and 6 months, and at the last visit after the treatment were analyzed.

Results: In total, 103 patients with 107 eyes were included. The mean age of the patients was 51.5±9.3 years, and 77 (72.0%) were male. The mean follow-up duration was 48.6±40.2 weeks. The mean duration of oral SPRL therapy was 15.5±13.4 weeks. CMT, SRF height, and SFCT improved significantly at 1, 3, and 6 months after SPRL therapy and at the last follow-up. BCVA, however, showed no significant change at any time point. The rate of complete resolution of SRF at 1 month was higher in those with chronic CSC than in those with acute CSC (21.1% vs. 6.0%, respectively). Recurrence occurred in 14 (13.1%) eyes after the complete resolution of SRF. Older age (p=0.001), a greater number of previous intravitreal bevacizumab injections (p=0.006), and poor initial visual acuity (p=0.048) were associated with recurrence. No permanent adverse effects were observed.

Conclusion: Oral SPRL showed therapeutic benefits in patients with CSC in terms of SRF resolution, but relatively frequent recurrence was observed, especially in older patients.

Key Words: Central serous chorioretinopathy, spironolactone, therapeutics

INTRODUCTION

Central serous chorioretinopathy (CSC) is characterized by localized detachment of the neurosensory retina and retinal pigment epithelium (RPE). Its incidence is estimated at 5.8 per 100000 people, predominantly men, who are affected at an incidence six times higher than that in women.[1] While the pathogenesis of CSC is still unclear, the development of subretinal fluid (SRF) is generally regarded as a source of disturbance of the RPE in association with increased choroidal vascular hyperpermeability and choroidal thickening.[2,3] The acute form of CSC shows a good prognosis in general, with spontaneous regression observed in approximately 60%–80% of the patients.[4,5] However, chronic or recurrent CSC can result in irreversible visual loss and RPE damage; hence, safe and effective treatment is critical.[4-7]

Several treatments, including systemic acetazolamide,[8] laser photocoagulation,[9] intravitreal anti-vascular endothelial growth factor injection,[10-12] and photodynamic therapy (PDT), either with full fluence or reduced fluence,[13-15] have been used to treat persistent CSC. A recent animal study, which reported the role of the mineralocorticoid receptor in vasodilation and leakage of choroidal vessels, prompted the use of oral mineralocorti-

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coid receptor antagonists (e.g., spironolactone and eplerenone) to treat CSC, with generally favorable outcomes.[16-21] However, their long-term effectiveness and safety profile have not been investigated in a large cohort of patients.

The purpose of this study was to investigate treatment outcomes, recurrence rates, and the safety of oral spironolactone (SPRL) in the management of CSC.

MATERIALS AND METHODS

This study was conducted as an interventional, open-label, retrospective study that included patients with CSC who were treated with SPRL in two tertiary referral centers (Severance Hospital and Gangnam Severance Hospital) between December 2015 and November 2018. This retrospective, observational study was approved by the Institutional Review Board of Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea (3-2019-0252).

We reviewed the medical records of 103 patients with CSC involving 107 eyes treated with oral SPRL. Patients with CSC in whom SRF involving the fovea was visualized on optical coherence tomography (OCT) were included. Patients with CSC who had choroidal neovascularization, polypoidal choroidal vasculopathy, and other macular involving diseases, such as retinal artery/vein occlusion or myopic degeneration, were excluded. Patients who received PDT, laser treatment, or intravitreal bevacizumab injections within the last 6 months were also excluded.

Oral SPRL (Aldactone; Pfizer, New York, NY, USA) was administered twice daily (50 mg/day) for 3 months or until SRF accumulation was resolved. If SRF resolved earlier than 3 months, the treatment was discontinued. If SRF persisted after 3 consecutive months, the attending physicians analyzed the patient's response to treatment to determine if the medication should be discontinued. Blood chemistry, including serum potassium and serum creatinine levels, was evaluated at baseline and at each follow-up visit until the discontinuation of the drug to assess drug tolerance. In cases where a follow-up visit occurred at less than 1 month after treatment began, the laboratory test was not conducted.

Patients visited the clinic at baseline, 1 month, and at an interval of 1–3 months thereafter, depending on the treatment outcomes. If a patient showed complete resolution of SRF, the follow-up visit was extended to 6 months or more. Complete ophthalmic examination included best corrected visual acuity (BCVA), slit lamp biomicroscopy, dilated fundus exam, fluorescein and indocyanine green angiography (HRA-2; Heidelberg Retina Angio-graph System; Heidelberg Engineering, Heidelberg, Germany), spectral-domain OCT, and enhanced-depth imaging OCT (SPECTRALIS; Heidelberg Engineering). Central macular thickness (CMT), SRF height, and subfoveal choroidal thickness (SFCT) were measured by spectral-domain OCT. CMT was defined as the mean thickness within the central grid (1 mm zone), as defined by the Early Treatment of Diabetic Retinopathy Study. SRF height was manually measured from the outer surface of the neurosensory retina to the inner surface layer of the RPE in the central fovea. SFCT was manually measured from the inner surface of the sclera to the outer surface of the RPE via enhanced-depth imaging OCT.

We classified the patients into two groups based on symptom duration before initiating treatment: those who had symptoms for less or more than 3 months were classified as acute and chronic groups, respectively. The two groups were compared with respect to the parameters mentioned above. Additionally, patients with complete resolution of SRF were classified into two groups based on recurrence: one group experienced recurrence of SRF and the other did not. We also classified the patients into three groups as complete responders (CR), partial responders (PR), and non-responders (NR). CR was defined as complete resolution of SRF. PR was defined as a more than 30% decrease in SRF height since the previous visit. NR was defined as a less than 30% decrease in SRF height since the previous visit.

Statistical analyses were performed using SPSS 25.0 (IBM Corp., Armonk, NY, USA). The treatment outcomes were evaluated at baseline, at 1, 3, and 6 months, and at the last follow-up. The paired t-test, independent t-test, chi-square test, Fisher's exact test, Mann-Whitney test, and linear mixed model were used to compare parameters at baseline with parameters after treatment. *P* values less than 0.05 were considered statistically significant.

RESULTS

In total, 107 eyes in 103 patients who were diagnosed with CSC and received oral SPRL were enrolled in this study. The mean age of the patients was 51.5±9.3 years; 77 (72.0%) were male. Before this study, 4 (3.7%) had taken systemic steroids, 13 (12.1%) had undergone focal laser photocoagulation, and 41 (38.3%) had received intravitreal bevacizumab injection. Fifty-eight (54.2%) eyes had no history of previous treatment. The mean duration of symptoms in the cohort was 17.7±25.4 weeks. Fifty (46.7%) eyes had acute CSC, and 57 (53.3%) had chronic CSC. The mean duration of follow-up was 48.6±40.2 weeks, and the mean duration of SPRL therapy was 15.5±13.4 weeks (Table 1).

CMT and SRF height significantly decreased after SPRL at all evaluation time points ($p<0.001$ in all, determined using the linear mixed model followed by Tukey's Honest Significant Difference test). CMT decreased from 395.4±119.8 μm at baseline to 320.9±87.1 μm, 292.5±80.9 μm, 275.3±67.3 μm, and 249.9±50.8 μm at 1, 3, and 6 months after treatment and the last visit, respectively. SRF decreased from 194.1±122.8 μm at baseline to 112.4±88.3 μm, 77.3±90.1 μm, 56.8±79.6 μm, and

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28.5±55.5 μm at 1, 3, and 6 months and the last visit, respectively. SFCT decreased from 418.1±108.0 μm at baseline to 407.4±107.9 μm (p=0.028), 383.1±105.2 μm (p<0.001), 353.5±100.2 μm (p<0.001), and 366.3±99.7 μm (p=0.002) at 1, 3, and 6 months and the last visit, respectively. There was a tendency for visual improvement after treatment, although this was not statistically significant at any timepoint. Complete resolution of SRF was achieved in 13.1%, 33.7%, 52.5%, and 81.2% of the patients at 1, 3, and 6 months and the last visit, respectively.

Fourteen (13.1%) eyes showed recurrence during the mean follow-up of 95.2±34.7 weeks. The mean interval between complete resolution of SRF to recurrence was 18.3±16.8 weeks. Old age (p=0.001), history of intravitreal bevacizumab injections (p=0.006), and poor initial visual acuity (p=0.048) were factors associated with recurrence (Table 2).

Table 1. Demographic and Clinical Characteristics of the Study Population

Characteristics	Values
Age, yr	51.5±9.3
Sex, males	77 (72.0)
Systemic conditions	
HTN	13 (12.6)
DM	7 (6.8)
Previous use of steroids, eyes	4 (3.7)
Previous treatments, eyes	
Laser photocoagulation	13 (12.1)
Intravitreal Bevacizumab	41 (38.3)
None	58 (54.2)
Duration of symptoms, weeks	17.7±25.4
Eyes with acute CSC (<12 weeks), eyes	50 (46.7)
Eyes with chronic CSC (≥12 weeks), eyes	57 (53.3)
Duration of follow up, weeks	48.6±40.2
Duration of SPRL therapy, weeks	15.5±13.4

HTN, hypertension; DM, diabetic mellitus; CSC, central serous chorioretinopathy; SPRL, spironolactone.
Data are presented as mean±standard deviation or n (%).

We analyzed the therapeutic effects of SPRL in the recurrence and non-recurrence groups. In the non-recurrence group, CMT and SRF showed significant improvement after SPRL treatment at all timepoints (p<0.001 at all timepoints). SFCT showed a significant change at 3 and 6 months and at the last visit (p=0.003, 0.005, and 0.006, respectively). BCVA showed significant improvement at 1 (p=0.017) and 6 months (p=0.048) after SPRL. In the recurrence group, CMT (p=0.001, 0.009, 0.009, and 0.002, respectively) and SRF height (p<0.001, p=0.004, 0.010, and 0.002, respectively) showed significant improvement at all timepoints, similar to those in the non-recurrence group. However, unlike those in the non-recurrence group, both BCVA and SFCT showed no significant change after SPRL at all timepoints in the recurrence group.

Therapeutic outcomes of oral SPRL therapy were analyzed in the acute and chronic groups. The patients with acute CSC were younger (p=0.001) and showed greater CMT (p<0.001), SRF height (p<0.001), and SFCT (p=0.002) at presentation. In both the acute and chronic CSC groups, CMT and SRF height decreased significantly at all the evaluation timepoints (p<0.001 each, determined using the linear mixed model followed by Tukey's Honest Significant Difference test), following oral SPRL. A statistically significant decrease in SFCT was observed at 3 months (p=0.049) in the acute CSC group, while it was observed at 1, 3, and 6 months in the chronic CSC group (p=0.016, p<0.001, and p=0.001, respectively). Visual acuity significantly improved at 1 month in the chronic CSC group (p=0.016), but not at other evaluation periods in both the acute and chronic CSC groups. Changes over time between acute and chronic CSC were not significantly different in regards to CMT, SRF, and BCVA. However, there was significant difference between the two groups in SFCT (p<0.001) (Fig. 1). The percentage of

Table 2. Comparison of Baseline Characteristics in Non-Recurred and Recurred Eyes

Characteristics	Non-recurred (n=93)	Recurred (n=14)	p value
Age, yr	50.5±9.2	58.6±6.6	0.001*
Sex, male	70 (75.3)	7 (50)	0.180†
Duration of symptom, weeks	15.7±21.8	33.4±43.2	0.233*
Previous use of steroids	4 (4.3)	0 (0)	1.000†
Previous treatments			
Laser	12 (12.9)	1 (7.1)	1.000†
Intravitreal anti-VEGF	31 (33.3)	10 (71.4)	0.006‡
Duration of medication, weeks	13.8±9.7	26.8±25.2	0.079*
Baseline CMT, μm	405.53±123.93	335.5±59.7	0.081*
Baseline SRF, μm	204.52±127.21	132.07±56.21	0.055*
Baseline SFCT, μm	425.29±101.66	367.29±134.71	0.060*
Baseline BCVA, logMAR	0.18±0.22	0.27±0.22	0.048*

VEGF; vascular endothelial growth factor; CMT, central macular thickness; SRF, subretinal fluid; SFCT, subfoveal choroidal thickness; BCVA, best-corrected visual acuity; logMAR, logarithm of the minimum angle of resolution.
Data are presented as mean±standard deviation or n (%).
*Independent t-test; †Fisher's exact test; ‡chi-square test.

eyes with complete SRF resolution gradually increased in both the acute and chronic CSC groups (Fig. 2).

There was a tendency for more eyes to achieve complete SRF resolution at 1 month in the chronic CSC group than in the acute CSC group (21.1% vs. 6.0%); however, the difference was not statistically significant (p=0.074). SRF resolution, for either

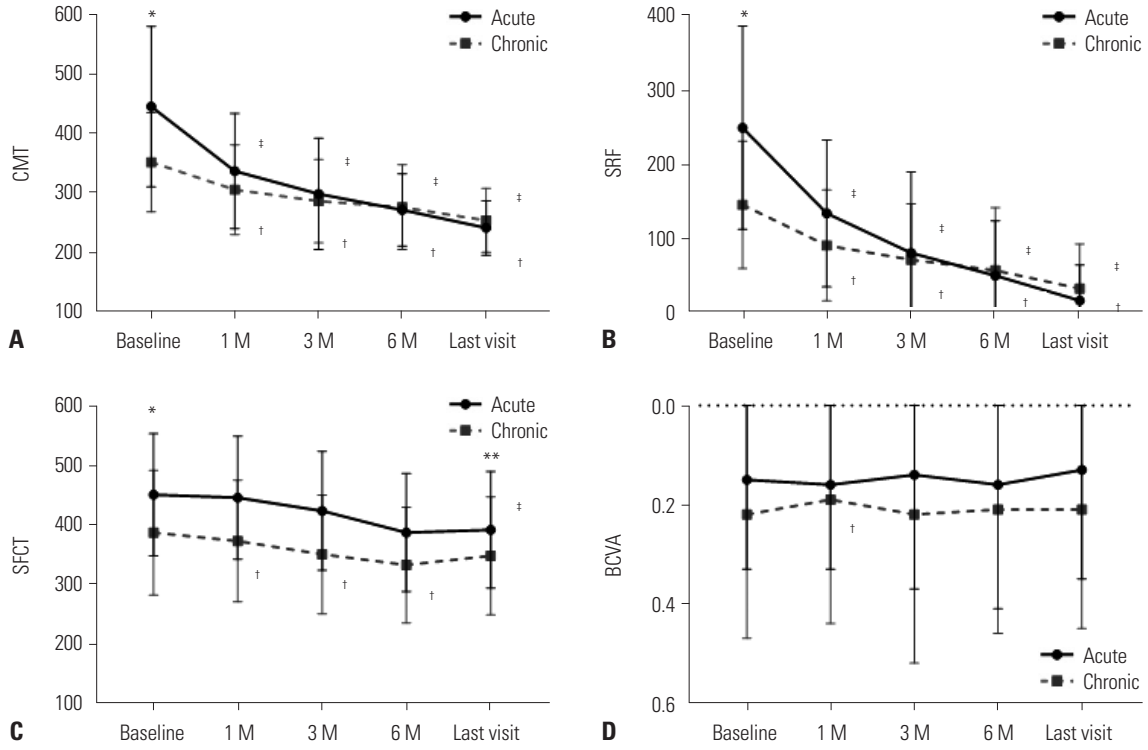

Fig. 1. Comparison of and changes in therapeutic outcomes in patients with acute and chronic central serous chorioretinopathy (CSC) after oral spironolactone. Graphs showing changes in (A) CMT, (B) SRF, (C) SFCT, and (D) BCVA. *p<0.05 at baseline between the two groups; **p<0.001 acute vs chronic determined with linear mixed model followed by Tukey's Honest Significant Difference test; †p<0.05 change from baseline in the chronic CSC group; ‡p<0.05 change from baseline in the acute CSC group. CMT, central macular thickness; SRF, subretinal fluids; SFCT, subfoveal choroidal thickness; BCVA, best-corrected visual acuity; M, months.

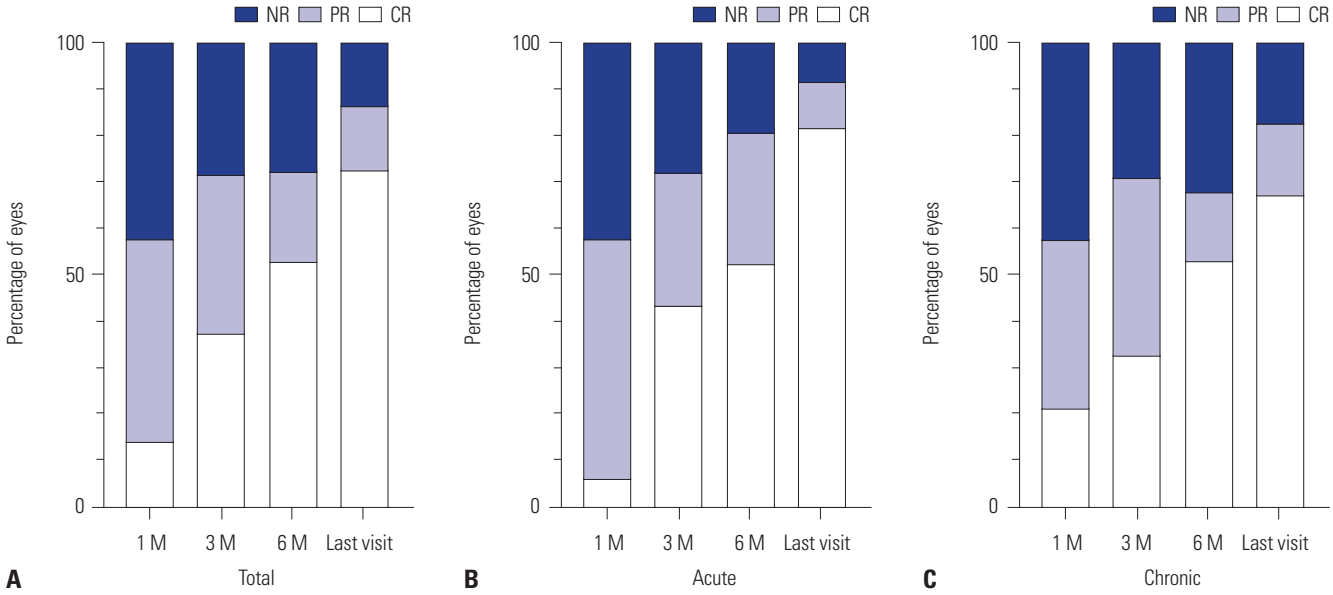

Fig. 2. Proportion of patients during follow-up in terms of subretinal fluid resolution. Bar graphs showing the proportion of (A) the total study cohort, (B) acute CSC group, and (C) chronic CSC group. CSC, central serous chorioretinopathy; NR, non-responder; PR, partial responder; CR, complete responder; M, months.

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including partial or complete resolution, at 1 month was not associated with SRF resolution at the last follow-up. SRF resolution (including partial or complete resolution) at 3 months was associated with CR (p=0.028) and PR or CR (p<0.001) at the last follow-up.

Two of the 77 (2.6%) male patients developed gynecomastia at 2 and 3 months after treatment. After discontinuation of the drugs, their symptoms resolved. One (0.9%) patient experienced mild elevation of serum creatinine 6 months after taking SPRL, which returned to normal after discontinuation of the medication. One (0.9%) patient reported alopecia at 1 month after treatment and discontinued the medication.

DISCUSSION

The results of this study showed that oral SPRL is associated with SRF resolution and a decrease in choroidal thickness in both acute and chronic CSC. Oral mineralocorticoid receptor antagonists, such as spironolactone and eplerenone, have been proposed for the treatment of CSC based on an animal study, which showed that mineralocorticoid receptor activation is associated with the pathogenesis of CSC.[21] Subsequently, many studies have reported the therapeutic benefit of oral mineralocorticoid receptor antagonists in CSC. Bousquet, et al.[16] reported that SPRL was effective in reducing SRF and SFCT in patients with CSC, with persistent SRF for at least 3 months, compared with placebo, and later found that oral mineralocorticoid receptor antagonists were more effective in eyes with a thicker baseline choroid.[17] Daruich, et al.[22] reported similar improvements in CMT and SRF at 1, 3, and 6 months in patients with persistent CSC, defined as non-resolving SRF for at least 4 months, after oral SPRL and eplerenone. Other prospective, placebo-controlled studies also reported significant improvements in SRF and CMT after SPRL and eplerenone treatment.[23,24] However, a recent prospective study found no difference between oral eplerenone and placebo in the treatment outcomes in CSC;[25] hence, further studies are warranted to confirm the treatment efficacy of mineralocorticoid receptor antagonists in the management of CSC, including a comparison study between SPRL and eplerenone.

Complete resolution of SRF was observed in 14.0%, 37.2%, 52.5%, and 72.5% of the patients in our study at 1, 3, and 6 months and the last visit, respectively. Our findings are in line with those of previous studies that reported complete resolution in approximately 38% of the patients with CSC at 3 months and 40%–50% at 6 months after oral mineralocorticoid receptor antagonists.[17,22] These rates are relatively lower than those in previous studies, which reported a complete resolution rate of 80% after half-fluence or half-dose of PDT,[26,27] although short-term results might be comparable between oral SPRL and half-dose PDT.[20] Moreover, oral mineralocorticoid receptor antagonists appear to show the greatest efficacy among past oral medications that have been tried in CSC, including beta blockers, *Helicobacter pylori* agents, omeprazole, rifampicin, methotrexate, aspirin, acetazolamide, mifepristone, melatonin, finasteride, ketoconazole, antioxidants, and curcumin phospholipid.[28] Meanwhile, we observed recurrence in 13% of the eyes after achieving complete resolution within a mean period of 18.3± 16.8 weeks. Herold, et al.[29] reported a higher recurrence rate of 48%, including eyes with non-resolving SRF after SPRL. In general, these recurrence rates might be higher than those after PDT, which range from 9% to 21%.[13,30,31] Factors associated with recurrence included older age, history of previous bevacizumab injections, and poorer initial visual acuity in this study. Older age could be associated with frequent recurrence because the repair capacity of RPE may decrease with aging.[4] A history of previous intravitreal bevacizumab and poorer initial visual acuity may indicate more chronic and recalcitrant disease that is more likely to recur. The presence of occult choroidal neovascularization has been reported in CSC, which can be detected on OCT angiography. OCT angiographic findings were not included in this study; hence, it is possible that eyes with CSC that harbored occult choroidal neovascularization could have been included. Also, eyes that were treated with and responded to bevacizumab could potentially have occult choroidal neovascularization, which could have led to the recurrence of SRF after oral SPRL treatment.

Despite anatomical improvement, significant visual improvement was not observed at all visits, except at 1 month after treatment in the chronic CSC group. Other studies reported visual improvements after oral SPRL or eplerenone treatment.[17,22-24] This might be due to a combined population in this study with both chronic and non-chronic CSC, while other studies included patients with non-chronic or non-resolving CSC alone. We analyzed patients with acute and chronic CSC separately, because acute CSC could spontaneously resolve within approximately 3 months. It might be argued that the 72.5% CR rate of acute CSC at the final visit in our study might not be solely due to the therapeutic effect of SPRL, because acute CSC reportedly spontaneously resolves in more than half of patients.[4,5] Many of the eyes with acute CSC in our study would have likely spontaneously recovered without treatment. However, it is unknown whether oral SPRL might have contributed to faster SRF resolution. The CR rate at the last visit was 66.7% in patients with chronic CSC. Considering that these eyes had persistent SRF for more than 3 months, spontaneous resolution of SRF is less likely; nevertheless, a relatively high proportion of patients achieved CR after oral SPRL. Interestingly, the proportion of CRs at 1 month after oral SPRL was higher in the chronic CSC patients, who also showed greater visual improvement, compared to the acute CSC patients. Whether oral mineralocorticoid receptor antagonists are particularly more effective in patients with chronic CSC needs to be validated in further studies.

Adverse events in this study included gynecomastia in two male patients and transient elevation of serum creatinine in

one. All adverse events resolved, however, after discontinuation of the drug without treatment. One male patient reported increasing hair loss after 1 month of SPRL use and discontinued the medication. It is not clear whether acute alopecia was associated with SPRL, since SPRL is known to slow androgen production; hence, it is sometimes used to treat androgenic alopecia.[32] Stress might have contributed to the development of CSC in that patient and may be a more plausible cause of alopecia. Other reported adverse events, including fatigue, dizziness, gastric discomfort, and hyperkalemia,[22,29] were not observed in our study.

Because of the retrospective study design, not all patients were followed-up on a regular basis until the last follow-up period. Because patients with previous PDT, laser treatment, or intravitreal bevacizumab within 6 months, who are likely to be chronic or recurrent patients, were excluded from the study, potential selection bias should be considered in taking our recurrence rate. Additionally, there was no control group. Despite these limitations, however, we reported real-life clinical data of a relatively large number of patients with acute and chronic CSC treated with oral SPRL.

Our study results indicate that oral SPRL results in anatomical improvements in both acute and chronic CSC with excellent safety profiles. Although PDT might be superior in terms of SRF resolution and recurrence, its high cost and invasiveness may make oral SPRL a better first-line treatment option, especially in eyes with persistent SRF.

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AUTHOR CONTRIBUTIONS

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