Predictive Factors of Response to Mineralocorticoid Receptor Antagonists in Nonresolving Central Serous Chorioretinopathy

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• PURPOSE: To assess the efficacy and safety of mineralocorticoid receptor antagonists (MRAs) in the treatment of nonresolving central serous chorioretinopathy (CSC) and to identify factors that are predictive of treatment response.

• DESIGN: Retrospective, multicenter, noncomparative, interventional case series.

• METHODS: Clinical and imaging data from consecutive patients with nonresolving CSC treated with eplerenone or spironolactone for 3 to 6 months between 2012 and 2016 were reviewed. Outcome measures included the resolution of foveal subretinal detachment (SRD), changes in SRD height, central macular thickness, subfoveal choroidal thickness, best corrected visual acuity, and the occurrence of adverse events assessed at 3 and 6 months. The response to treatment was defined by a decrease by >50% in SRD height under treatment. Comparisons between responder and nonresponder groups were performed using univariate and multivariate regression analyses to identify factors that were predictive of treatment response.

• RESULTS: Fifty-nine patients (64 eyes) were included. The mean SRD height and central macular thickness significantly decreased while the mean best corrected visual acuity significantly improved at 3 and 6 months. The mean subfoveal choroidal thickness significantly decreased at 3 months. Among the 64 eyes included, 67.2% responded to treatment, among which 38.3% and 40.5% had a complete resolution of the foveal SRD at 3 and 6 months, respectively.

Baseline subfoveal choroidal thickness was the only factor associated with a treatment response in the multivariate analysis.

• CONCLUSION: Our study suggests that MRA could be a safe and effective treatment in patients with nonresolving CSC. MRA treatment is more effective in cases with a thicker baseline choroid. (Am J Ophthalmol 2019;198:80–87. © 2018 Elsevier Inc. All rights reserved.)

CENTRAL SEROUS CHORIORETINOPATHY (CSC) IS A common cause of central vision loss, the incidence of which is estimated at 1 case per 10,000 people, affecting predominantly middle-aged men.[1] The acute form of the disease resolves spontaneously within 4 months with good visual outcome. Chronic CSC is characterized by persistent serous retinal detachment that is often associated with widespread retinal pigment epithelium (RPE) alterations leading to photoreceptor damage and permanent vision loss.[2]

To date, there is no consensus for the management of nonresolving or chronic CSC. Several treatments have been proposed. Laser photocoagulation of a focal leakage outside the fovea detected by fluorescein angiography can accelerate the resolution of subretinal detachment (SRD).[3] Half-fluence or half-dose photodynamic therapy (PDT) is effective in reducing subretinal fluid duration and improving visual acuity, but some adverse events, such as choroidal neovascularization, RPE atrophy, or rip, have been reported.[4,5]

Although the exact pathogenesis of CSC is currently unknown, clinical and experimental studies suggest involvement of the steroid pathway. Corticosteroid exposure after therapeutic administration or endogenous overproduction, such as in Cushing syndrome, are associated with CSC.[6,7] Recently, involvement of the mineralocorticoid receptor (MR) has been hypothesized in the pathogenesis of CSC based on the results of studies conducted in rat eyes. Indeed, inappropriate MR activation by glucocorticoids upregulates the vasodilator potassium channel KCa2.3 and induces smooth muscle cell relaxation in choroidal vessels, resulting in the induction of choroidal thickening and subretinal fluid in rodents.[2,8] van Dijk and associates have published a genetic study showing that known variants of the MR gene were associated with an increased risk for CSC, supporting a possible role of MR in the pathogenesis of the disease.[9]

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Based on experimental results, 2 MR antagonists (MRAs), eplerenone and spironolactone, have been proposed to treat nonresolving CSC with variable response rates in one-third to two-thirds of patients with CSC.[10–15]

The aim of the study was to assess the effect of MRAs in a large cohort of patients and to identify possible predictive factors for treatment response.

METHODS

• **STUDY DESIGN:** This was an interventional, retrospective, noncomparative, open-label, multicenter clinical trial including patients with nonresolving CSC who were treated with eplerenone or spironolactone between May 2012 and September 2016 in the Ophthalmology Department of Lariboisière, Hôtel Dieu or xvxx hospitals in Paris, France. The off-label prescription and the potential benefits and risks of the treatment were discussed with all patients and informed consent was obtained. This study was conducted in compliance with the tenets of the Declaration of Helsinki and was approved by our institutional review board (CEERB d'Ile de France, Paris, France).

• **PATIENTS:** Patients with nonresolving CSC with foveal SRD for >3 months who were treated with oral eplerenone or spironolactone for ≥3 months were included in the study.

Exclusion criteria were (1) the presence of any other retinal disease, including age-related macular degeneration, diabetic retinopathy, retinal artery/vein occlusion, or high myopia; (2) history of CSC treatment, including laser, PDT, anti–vascular endothelial growth factor therapy in the year before inclusion; (3) follow-up <3 months; and (4) poor compliance with treatment. The presence of choroidal neovascularization detected by optical coherence tomography (OCT) angiography was not an exclusion criterion.

• **STUDY PROTOCOL:** Patient medical records and imaging data were reviewed at baseline, 3 months, and 6 months, including best corrected visual acuity (BCVA) converted into logMAR scale, dilated fundus biomicroscopy, and multimodal imaging data including spectral-domain OCT (Heidelberg Spectralis, Heidelberg, Germany), fundus autofluorescence, fluorescein angiography and, in most cases, indocyanine green angiography (ICGA; Spectralis). The SRD height was assessed by manually measuring the distance between the external limiting membrane and the RPE at the fovea. The central macular thickness (CMT) was recorded in the 1-mm diameter circle of the Early Treatment Diabetic Retinopathy Study (ETDRS) grid. Choroidal thickness (CT) was manually measured between the outer portion of the RPE and the inner surface of the sclera on enhanced depth imaging (EDI) horizontal B-scans. CT was measured at the fovea and at 1000 μm nasal and temporal to the fovea as previously described.[11] The subretinal fluid height and CT were measured by 2 independent graders (E.B., M.D.).

• **TREATMENT PROTOCOL:** Patients were treated with oral eplerenone (Inspra; Pfizer, New York, NY, USA) or spironolactone (Aldactone; Pfizer) at a dose of 25 mg per day for 1 week followed by 50 mg per day for 3 or 6 months depending on the presence or the absence of SRD. Kalemia and creatininemia were measured at baseline, 1 week, and every month. In cases with hyperkalemia or decreased creatinine clearance, treatment was discontinued.

• **RESPONDER AND NONRESPONDER GROUPS:** All patients were examined at baseline and at 3 months. Treatment was continued for 3 additional months in cases with persistent SRD. These patients were reassessed at 6 months.

Based on the response to treatment, patients were divided into 2 study groups. Patients without subretinal fluid or with a decrease of >50% in SRD height were considered responders. Patients with a decrease of <50% in SRD height were considered nonresponders.

• **STATISTICAL ANALYSES:** Descriptive data are presented as the mean ± standard deviation (SD) for quantitative variables and as counts and percentages for categorical variables. Comparisons between variables were performed using the Wilcoxon paired, Mann-Whitney *U*, and χ^2 tests when appropriate. A multivariate logistic regression analysis was used to identify independent factors of response to treatment. A receiver operating characteristic (ROC) curve was plotted using the subfoveal CT for predicting treatment response. The optimal cutoff was found using the Youden index. $P \leq .05$ was considered to be statistically significant. Statistical analyses were performed using XLstat software (version 2014.6.01; Addinsoft, Paris, France).

RESULTS

• **PATIENT CHARACTERISTICS:** Among the 71 patients with CSC treated with MRA over the study period, 64 eyes of 59 patients (53 men and 6 women) met the inclusion criteria. The mean ± SD patient age was 53.7 ± 12.4 years. A previous or ongoing use of corticosteroids was reported in 25 patients (42.4%). The mean ± SD visual symptom duration before treatment was 9.8 ± 9.2 months. Most patients (52/59, 88.1%) were treated with eplerenone, 7 patients (11.9%) received spironolactone, and 3 patients (5.1%) first received eplerenone and then spironolactone. All patients were treated for ≥3 months, and 41 patients (42 eyes) were treated for 6 months.

TABLE 1. Visual Acuity and Optical Coherence Tomography Data During the Follow-Up of Patients With Nonresolving Central Serous Chorioretinopathy Treated With Mineralocorticoid Receptor Antagonists

	Baseline, n = 64 Eyes	3 Months, n = 60 Eyes	6 Months, n = 42 Eyes
Foveal subretinal detachment resolution, n (%)		23 (38.3)	17 (40.5)
Best corrected visual acuity, logMAR, mean ± SD (Snellen)	0.34 ± 0.29 (20/40)	0.26 ± 0.29 (20/32) ($P < .0001$)	0.26 ± 0.30 (20/32) ($P = .016$)
Foveal subretinal detachment (μm), mean ± SD	211.1 ± 121.2	102.2 ± 112 ($P < .0001$)	94.5 ± 99 ($P < .0001$)
Central macular thickness (μm), mean ± SD	383.2 ± 122.7	294.1 ± 99.7 ($P < .0001$)	280.2 ± 80.8 ($P < .0001$)
Subfoveal choroidal thickness (μm), mean ± SD	445.8 ± 139.8 (16 unknown)	426.6 ± 135.9 ($P = .029$) (18 unknown)	413.5 ± 138.2 ($P = .055$) (12 unknown)

P values compared with baseline; paired *t* or Wilcoxon paired signed-rank test.

• **TREATMENT EFFECT:** A decrease of >50% in SRD height was observed in 43 of 64 eyes (67.2%) after 3 to 6 months of treatment that corresponded to the responder group. In this group, subfoveal SRD completely resorbed in 38.3% of eyes at 3 months and in 40.5% of eyes at 6 months (Table 1).

Among patients treated for 3 months with a complete resolution of the subfoveal SRD, a recurrence of SRD was detected in 2 eyes 2 and 3 months after treatment discontinuation.

No treatment response was observed in 21 of 64 eyes (32.8%) that corresponded to the nonresponder group.

Visual acuity values and OCT findings of all patients at 3 and 6 months are summarized in Table 1. The BCVA increased significantly from 0.34 ± 0.29 logMAR (20/40) at baseline to 0.26 ± 0.29 logMAR (20/32) at 3 months ($P < .0001$) and 0.26 ± 0.30 logMAR (20/32) at 6 months ($P = .016$).

The OCT analysis showed that the foveal SRD decreased significantly from 211.1 ± 121.2 μm at baseline to 102.2 ± 112 μm at 3 months ($P < .0001$) and 94.5 ± 99 μm at 6 months ($P < .0001$). The CMT decreased significantly from 383.2 ± 122.7 μm at baseline to 294.1 ± 99.7 μm at 3 months ($P < .0001$) and 280.2 ± 80.8 μm at 6 months ($P < .0001$).

The CT measurement was possible in 42 eyes at 3 months and in 30 eyes at 6 months. The subfoveal CT decreased from 445.8 ± 139.8 μm at baseline to 426.6 ± 135.9 μm at 3 months ($P = .029$) and 413.5 ± 138.2 μm at 6 months ($P = .055$).

• **COMPARISON OF CHARACTERISTICS BETWEEN RESPONDERS AND NONRESPONDERS:** Baseline clinical and imaging data comparisons between both groups are shown in Table 2.

Subfoveal and temporal CT were higher in the responder group compared with the nonresponder group ($P = .005$; Table 2, Figures 1 and 2). Moreover, the rates of previous/ongoing corticosteroid intake and gravitational tracks were significantly different between both groups. A history of corticosteroid intake was less common and the rate of gravitational tracks was higher in the responder group than in the nonresponder group ($P = .03$).

There were no statistically significant differences in age, sex ratio, symptom duration, visual acuity, subretinal fluid height, hyperpermeability identified on ICGA, and rate of CNV detected by OCT angiography.

Using multiple logistic regression analysis, a baseline subfoveal CT >515 μm was the only factor associated with the treatment response (odds ratio 15.8 [95% confidence interval 1.6-155.4]; $P = .018$; Table 3). A ROC curve analysis revealed that the optimal cutoff value (Younden index) was achieved with a subfoveal CT of 515 μm (sensitivity 94.4%, specificity 53.3%, area under the ROC curve 0.73, $P = .006$; Supplemental Figure, Supplemental Material at AJO.com). Indeed, in the responder group, 16 of 30 eyes (53.3%) had a subfoveal choroidal thickness (SFCT) >515 μm, while 1 of 18 eyes (5.6%) had a SFCT >515 μm in the nonresponder group ($P = .001$). In addition, among the 17 eyes with SFCT >515 μm, 16 (94.1%) were in the responder group while 1 (5.9%) was in the nonresponder group.

These results suggest that a thick subfoveal CT could be considered a favorable factor of response to MRA treatment.

• **TREATMENT TOLERANCE:** Overall, 9 patients experienced adverse events. Among the 52 patients treated with eplerenone, 6 (11.5%) patients reported adverse events as follows: hyperkalemia (n = 3), sudation (n = 1), asthenia (n = 1), and constipation (n = 1). Among the 7 patients treated with spironolactone, 3 (42.9%) patients experienced adverse events: increased creatinine level (n = 1), hyperkalemia (n = 1), and

TABLE 2. Comparison of Baseline Clinical and Imaging Data Between Responders and Nonresponder Patients With Nonresolving Central Serous Chorioretinopathy Treated With Mineralocorticoid Receptor Antagonists

	Responder Group, 39 Patients (43 Eyes)	Nonresponder Group, 20 Patients (21 Eyes)	*P* Value
Age (y), mean ± SD	54.5 ± 12.1	52.2 ± 13	.3[a]
Male, n (%)	34 (87.2)	19 (95)	.3[b]
Patients with previous or ongoing corticosteroid intake, n (%)	14 (38.9) (3 unknown)	11 (61.1) (2 unknown)	.03[c]
Symptom duration (months), mean ± SD	9.6 ± 9.4	10.3 ± 8.9	.8[a]
BCVA, logMAR, mean ± SD (Snellen)	0.37 ± 0.3 (20/50)	0.30 ± 0.3 (20/40)	.3[a]
Subretinal detachment height (μm), mean ± SD	214.6 ± 132.8	194.1 ± 85.6	.5[a]
Subfoveal choroidal thickness (μm), mean ± SD	501 ± 148 (13 unknown)	385.3 ± 95.8 (3 unknown)	.005[a]
Subfoveal choroidal thickness >515 μm, n (%)	16/30 (53.3)	1/18 (5.6)	.001[c]
1000 μm temporal choroidal thickness (μm), mean ± SD	467.2 ± 158.1	347.2 ± 73.9	.005[a]
1000 μm nasal choroidal thickness (μm), mean ± SD	446.7 ± 143.7	366.9 ± 104.5	.06[a]
Autofluorescence: gravitational tracks, number of eyes, (n) %	23 (54.8) (1 unknown)	5 (25) (1 unknown)	.03[c]
ICGA: intermediate hyperfluorescent area, n (%)	33 (82.5) (3 unknown)	11 (57.9) (2 unknown)	.09[b]
CNV detected by OCT-A, n (%)	2 (5.9) (9 unknown)	4 (25) (5 unknown)	.07[d]

BCVA = best corrected visual acuity; CNV = choroidal neovascularization; ICGA = indocyanine green angiography; OCT-A = optical coherence tomography angiography; SD = standard deviation.

[a]Student *t* test.

[b]χ^2 test with Yates' continuity correction.

[c]χ^2 test.

[d]Fisher exact test.

gynecomastia (n = 1). All complications resolved after treatment discontinuation.

DISCUSSION

THIS STUDY INCLUDED THE LARGEST COHORT OF PATIENTS treated with oral MRA for nonresolving CSC, with collection of data from 3 different ophthalmology departments.

Spironolactone and eplerenone have been proposed for the treatment of CSC based on experimental and animal studies demonstrating the potential role of MR activation in the pathogenesis of the disease.[8]

To date, several published studies have reported the outcomes of MRA treatment in patients with CSC, with variable results in terms of SRD resolution. Most were retrospective studies. To our knowledge, only 4 randomized, controlled, prospective studies have been published.[11,16–18] The first was a prospective, randomized, placebo-controlled study with a crossover design assessing spironolactone treatment in 16 patients with chronic CSC. A statistically significant reduction in SRD and CT was detected in the spironolactone group compared with the placebo group.[11] Recently, 2 other prospective, randomized, placebo-controlled studies have supported these results by showing a statistically significant reduction in SRD, CMT, and an increase in BCVA in the eplerenone and spironolactone groups compared with the placebo group.[17,18] However, Schwartz and associates, in another randomized, placebo-controlled study in 17 patients (19 eyes), have shown no differences in SRD reduction between patients treated with eplerenone and the placebo.[16] This discrepancy could be caused by differences in study protocol, inclusion criteria, and small sample sizes. The efficacy of the treatment remains to be confirmed in additional randomized controlled studies.

In our study, MRA treatment significantly decreased SRD in 67% of patients; 33% of patients did not respond to treatment. A complete resolution of foveal SRD was observed in 38.3% and 40.5% of cases at 3 and 6 months,

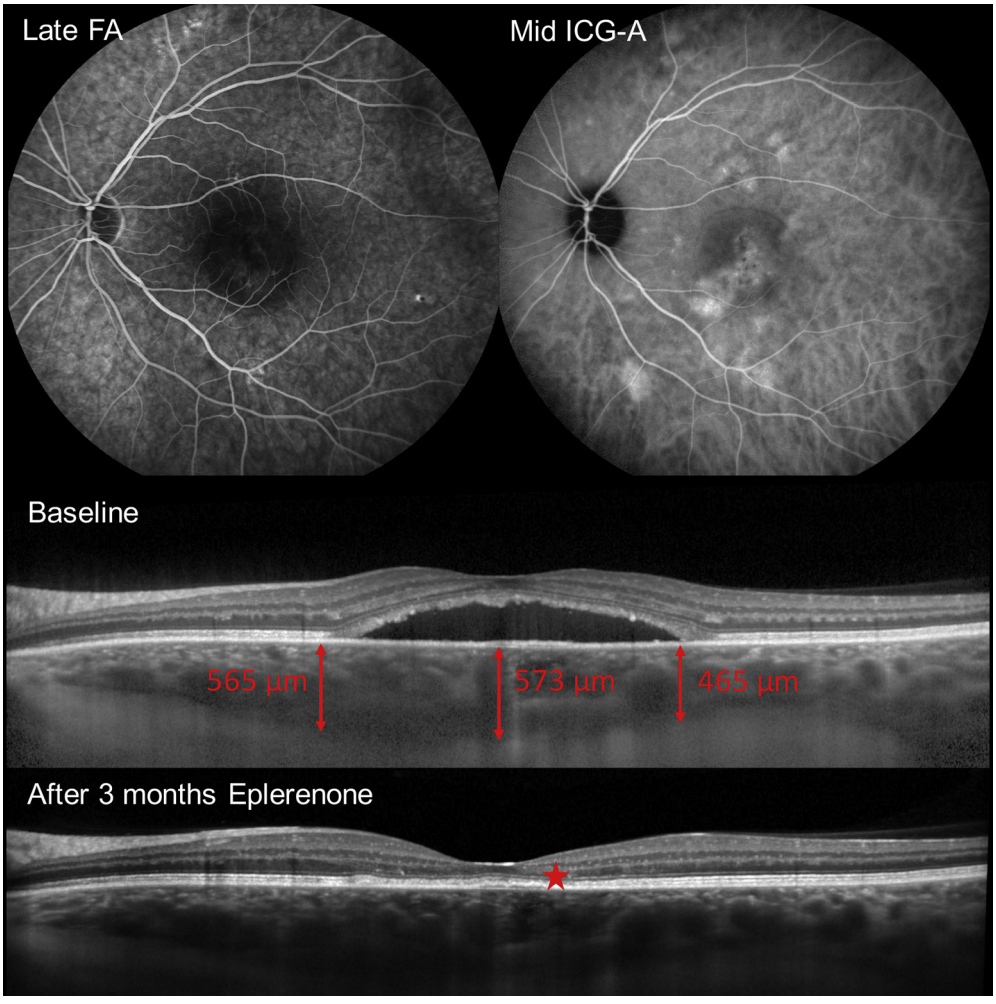

FIGURE 1. Multimodal images of a 49-year-old man with nonresolving central serous chorioretinopathy for 4 months without improvement. (Top left) Late-phase fluorescein angiography (FA) shows no leaking point. (Top right) Mid-phase indocyanine green angiography (ICG-A) shows several areas of hyperfluorescence of choroidal hyperpermeability. (Middle) Horizontal enhanced depth optical coherence tomography imaging centered on the fovea shows a foveal subretinal detachment associated with an increased choroidal thickness (subfoveal: 573 µm; 1000 µm nasal: 565 µm; 1000 µm temporal: 465 µm). (Bottom) Horizontal enhanced depth optical coherence tomography imaging centered on the fovea 3 months after initiation of eplerenone treatment (50 mg/day) shows a complete resolution of the subretinal detachment with a thinning of the outer nuclear layer (star).

respectively. Subfoveal CT decreased and visual acuity improved under treatment. These results are in line with previous research.[15,17] Indeed, in a retrospective study including 42 patients (54 eyes), Daruich and associates have observed a complete resolution of foveal SRD in 38% and 50% of eyes at 3 and 6 months, respectively.[15]

In comparison, the rate of SRD resolution reported after half-fluence or half-dose PDT is higher and observed in almost 80% to 96% of cases.[5,19,20] Indeed, Fujita and associates have assessed 204 patients with chronic CSC treated with half-dose PDT. A complete resolution of SRD was obtained in 89.2% of cases at 12 months.[20] Otherwise, to our knowledge, there is only 1 recently published study comparing the efficacy and safety of MRA with half-dose PDT for the treatment of nonresolving CSC.[21] A complete regression of SRD was observed in 38.9% of patients in the spironolactone group and in 56.5% of patients in the PDT group at 3 months. The difference was not statistically significant between both groups, possibly because of small sample sizes. However, a significant decrease in CT was observed in the PDT group while no change was detected in the spironolactone group.[21] In fact, several studies have shown that the CT rapidly decreases after successful half-fluence or half-dose PDT with a 3-month reduction ranging between 54 and 89 µm according to studies.[22–26] Changes in CT under MRA treatment remain controversial. In our study, we found a significant decrease in CT after 3 months of treatment in accordance with 3 previous studies,[11,13,15] while other groups have not found any changes in CT.[14,21] It is worth noting that a reduction in CT by approximately 30 µm has also been

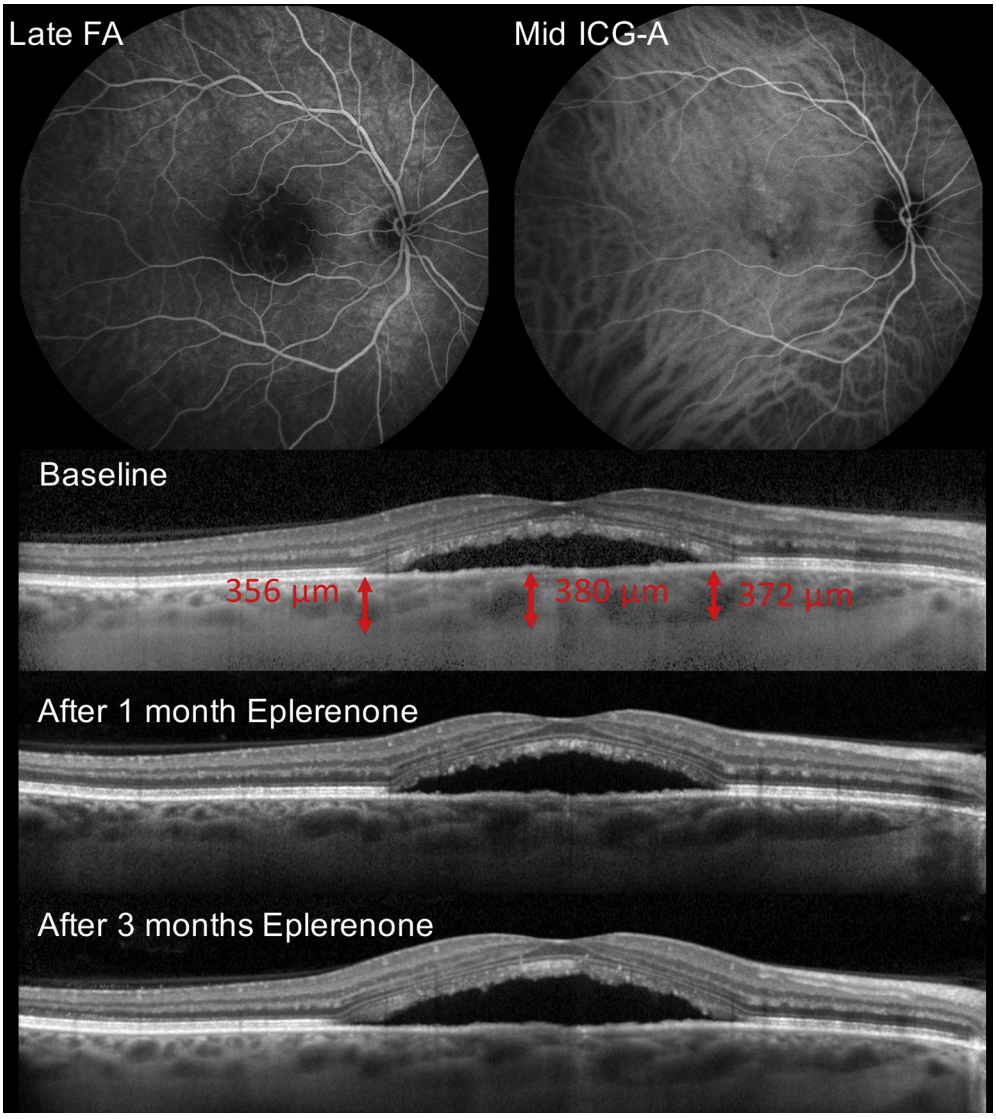

FIGURE 2. Multimodal images of a 47-year-old man with nonresolving central serous chorioretinopathy for 4 months without improvement. (Top left) Late-phase fluorescein angiography (FA) shows no leaking point. (Top right) Mid-phase indocyanine green angiography (ICG-A) shows a foveal area of hyperfluorescence. (Second row) Horizontal enhanced depth optical coherence tomography imaging centered on the fovea shows a foveal subretinal detachment associated with a subfoveal choroidal thickness assessed at 380 µm (1000 µm nasal: 372 µm; 1000 µm temporal: 356 µm). (Third row-bottom) Horizontal enhanced depth optical coherence tomography imaging centered on the fovea 1 month (third row) and 3 months (bottom) after initiation of eplerenone treatment (50 mg/day) shows no decrease in subretinal detachment.

described in cases with spontaneous resolution of CSC.[27] Gergely and associates have assessed CT in 28 eyes with SRD and fellow eyes without SRD in patients with CSC who were treated with eplerenone. At 3 months, they have reported a 28-µm decrease in eyes with SRD and an 8-µm decrease in eyes without SRD, suggesting a small effect of eplerenone on CT[13] unlike half-fluence PDT.

In addition, we investigated the presence of potential predictive factors for treatment response and found that a thick choroid was the only factor associated with treatment response in the multivariate analysis. In the responder group, 16 of 30 eyes (53.3%) had a subfoveal CT >515 µm, while 1 of 18 eyes (5.6%) had a subfoveal CT >515 µm in the nonresponder group ($P = .001$). On the other hand, in patients with subfoveal CT >515 µm, 16 of 17 (94.1%) responded to treatment. This result supports the findings of Gergely and associates study showing that the baseline CT was a positive predictor for SRD decrease under eplerenone treatment in the multivariate analysis.[13]

Until recently, the ocular bioavailability of MRA after systemic administration was unknown. Spironolactone induces the expression of P-glycoprotein,[28] a drug efflux protein that regulates the blood retinal barrier and could reduce its ocular bioavailability. Indeed, after intravenous

TABLE 3. Multiple Logistic Regression Analysis of Factors Associated With Response to Mineralocorticoid Receptor Antagonists in Patients With Nonresolving Central Serous Chorioretinopathy

	Beta	OR (95% CI)	*P* Value
Previous or ongoing corticosteroid intake	−0.173	0.5 (0.1-2.3)	.717
Subfoveal choroidal thickness >515 μm	0.738	15.8 (1.6-155.4)	.018
Autofluorescence: gravitational tracks	0.061	1.3 (0.2-7.5)	.799

CI = confidence interval; OR = odds ratio.

injection of spironolactone in rodents, spironolactone and its metabolites were below detectable levels in the vitreous.[29] The effect of treatment could partly result from the effect on choroidal vessels but also from spironolactone penetration through the RPE barrier breakdown.[29] In our study, the treatment was more effective in patients with a thicker choroid, possibly because of the effect of the drug on choroidal vessels.

In a recent study, Sacconi and associates have assessed predictive biomarkers of treatment outcomes using multimodal imaging in patients treated with eplerenone.[30] The absence of CNV on OCT-A and the presence of hot spot on ICGA were associated with a good response to treatment. Interestingly, in our study, 25% of patients in the nonresponder group had CNV detected by OCT-A compared with 5.9% of patients in the responder group ($P = .07$). The difference was not statistically significant, possibly because OCT-A images were not available in 14 patients, which reduced the sample size. Nevertheless, our results are consistent with those of Sacconi and associates, and the presence of CNV could be considered a factor of poor response to treatment.

Treatment with eplerenone was generally well tolerated in our study. A higher number of adverse events was reported after the use of spironolactone compared with eplerenone (42.9% vs 11.1%). Eplerenone is a MRA with a higher affinity and selectivity for MR than spironolactone that also binds to progesterone and androgen receptors, leading to hormonal adverse events (gynecomastia, erectile dysfunction, and loss of libido).[31] No ocular side effects were observed under MRA treatment. In comparison, while the complication rate following half-dose or half-fluence PDT is generally low, RPE atrophy, RPE rip, or CNV may occur in a small percentage of cases.[5]

This study has some limitations, including its retrospective design, the absence of a placebo-treated group, the use of 2 drugs, and the short follow-up duration. Nevertheless, this study suggests that MRA treatment is more effective in patients with a thick choroid at baseline (ie, subfoveal CT >515 μm). Considering the high cost of PDT, MRA could be used as an alternative treatment in selected cases of nonresolving CSC.

In summary, although additional prospective, controlled studies in large cohorts are needed to confirm these results and determine the optimal dose/duration of treatment, our results suggest a potential high response rate to MRA in patients with a thick choroid.

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REFERENCES

1. Kitzmann AS, Pulido JS, Diehl NN, Hodge DO, Burke JP. The incidence of central serous chorioretinopathy in Olmsted County, Minnesota, 1980-2002. *Ophthalmology* 2008;115(1):169–173.
2. Daruich A, Matet A, Dirani A, et al. Central serous chorioretinopathy: recent findings and new physiopathology hypothesis. *Prog Retin Eye Res* 2015;48:82–118.
3. Robertson DM, Ilstrup D. Direct, indirect, and sham laser photocoagulation in the management of central serous chorioretinopathy. *Am J Ophthalmol* 1983;95(4):457–466.
4. Chan W-M, Lai TYY, Lai RYK, Liu DTL, Lam DSC. Half-dose verteporfin photodynamic therapy for acute central serous chorioretinopathy: one-year results of a randomized controlled trial. *Ophthalmology* 2008;115(10):1756–1765.
5. Lai FHP, Ng DS, Bakthavatsalam M, et al. A multicenter study on the long-term outcomes of half-dose photodynamic therapy in chronic central serous chorioretinopathy. *Am J Ophthalmol* 2016;170:91–99.
6. Bouzas EA, Karadimas P, Pournaras CJ. Central serous chorioretinopathy and glucocorticoids. *Surv Ophthalmol* 2002;47(5):431–448.

7. Bousquet E, Dhundass M, Lehmann M, et al. Shift work: a risk factor for central serous chorioretinopathy. *Am J Ophthalmol* 2016;165:23–28.
8. Zhao M, Célérier I, Bousquet E, et al. Mineralocorticoid receptor is involved in rat and human ocular chorioretinopathy. *J Clin Invest* 2012;122(7):2672–2679.
9. van Dijk EHC, Schellevis RL, van Bergen MGJM, et al. Association of a haplotype in the NR3C2 gene, encoding the mineralocorticoid receptor, with chronic central serous chorioretinopathy. *JAMA Ophthalmol* 2017;135(5):446–451.
10. Bousquet E, Beydoun T, Zhao M, Hassan L, Offret O, Behar-Cohen F. Mineralocorticoid receptor antagonism in the treatment of chronic central serous chorioretinopathy: a pilot study. *Retina* 2013;33(10):2096–2102.
11. Bousquet E, Beydoun T, Rothschild P-R, et al. Spironolactone for nonresolving central serous chorioretinopathy: a randomized controlled crossover study. *Retina* 2015;35(12):2505–2515.
12. Cakir B, Fischer F, Ehlken C, et al. Clinical experience with eplerenone to treat chronic central serous chorioretinopathy. *Graefes Arch Clin Exp Ophthalmol* 2016;254(11):2151–2157.
13. Gergely R, Kovács I, Schneider M, et al. Mineralocorticoid receptor antagonist treatment in bilateral chronic central serous chorioretinopathy: a comparative study of exudative and nonexudative fellow eyes. *Retina* 2017;37(6):1084–1091.
14. Ghadiali Q, Jung JJ, Yu S, Patel SN, Yannuzzi LA. Central serous chorioretinopathy treated with mineralocorticoid antagonists: a one-year pilot study. *Retina* 2016;36(3):611–618.
15. Daruich A, Matet A, Dirani A, et al. Oral mineralocorticoid-receptor antagonists: real-life experience in clinical subtypes of nonresolving central serous chorioretinopathy with chronic epitheliopathy. *Transl Vis Sci Technol* 2016;5(2):2.
16. Schwartz R, Habot-Wilner Z, Martinez MR, et al. Eplerenone for chronic central serous chorioretinopathy-a randomized controlled prospective study. *Acta Ophthalmol* 2017;95(7):e610–e618.
17. Rahimy E, Pitcher JD, Hsu J, et al. A randomized double-blind placebo-control pilot study of eplerenone for the treatment of central serous chorioretinopathy (ecselsior). *Retina* 2018;38(5):962–969.
18. Sun X, Shuai Y, Fang W, et al. Spironolactone versus observation in the treatment of acute central serous chorioretinopathy. *Br J Ophthalmol* 2018;102(8):1060–1065.
19. Inoue R, Sawa M, Tsujikawa M, Gomi F. Association between the efficacy of photodynamic therapy and indocyanine green angiography findings for central serous chorioretinopathy. *Am J Ophthalmol* 2010;149(3):441–446. e1-2.
20. Fujita K, Imamura Y, Shinoda K, et al. One-year outcomes with half-dose verteporfin photodynamic therapy for chronic central serous chorioretinopathy. *Ophthalmology* 2015;122(3):555–561.
21. Lee JH, Lee SC, Kim H, Lee CS. Comparison of short-term efficacy between oral spironolactone treatment and photodynamic therapy for the treatment of nonresolving central serous chorioretinopathy. Retina (forthcoming).
22. Haga F, Maruko R, Sato C, Kataoka K, Ito Y, Terasaki H. Long-term prognostic factors of chronic central serous chorioretinopathy after half-dose photodynamic therapy: A 3-year follow-up study. *PLoS One* 2017;12(7):e0181479.
23. Kinoshita T, Mitamura Y, Mori T, et al. Changes in choroidal structures in eyes with chronic central serous chorioretinopathy after half-dose photodynamic therapy. *PLoS One* 2016;11(9):e0163104.
24. Hua R, Liu L, Li C, Chen L. Evaluation of the effects of photodynamic therapy on chronic central serous chorioretinopathy based on the mean choroidal thickness and the lumen area of abnormal choroidal vessels. *Photodiagn Photodyn Ther* 2014;11(4):519–525.
25. Uetani R, Ito Y, Oiwa K, Ishikawa K, Terasaki H. Half-dose vs one-third-dose photodynamic therapy for chronic central serous chorioretinopathy. *Eye* 2012;26(5):640–649.
26. Maruko I, Iida T, Sugano Y, Furuta M, Sekiryu T. One-year choroidal thickness results after photodynamic therapy for central serous chorioretinopathy. *Retina* 2011;31(9):1921–1927.
27. Chung Y-R, Kim JW, Choi S-Y, Park SW, Kim JH, Lee K. Subfoveal choroidal thickness and vascular diameter in active and resolved central serous chorioretinopathy. *Retina* 2018;38(1):102–107.
28. Ghanem CI, Gómez PC, Arana MC, et al. Induction of rat intestinal P-glycoprotein by spironolactone and its effect on absorption of orally administered digoxin. *J Pharmacol Exp Ther* 2006;318(3):1146–1152.
29. Zhao M, Rodríguez-Villagra E, Kowalczuk L, et al. Tolerance of high and low amounts of PLGA microspheres loaded with mineralocorticoid receptor antagonist in retinal target site. *J Control Release* 2017;266:187–197.
30. Sacconi R, Baldin G, Carnevali A, et al. Response of central serous chorioretinopathy evaluated by multimodal retinal imaging. *Eye* 2018;32(4):734–742.
31. Cook CS, Berry LM, Bible RH, Hribar JD, Hajdu E, Liu NW. Pharmacokinetics and metabolism of [14C]eplerenone after oral administration to humans. *Drug Metab Dispos* 2003;31(11):1448–1455.