·Clinical Research·

Clinical research of fenofibrate and spironolactone for acute central serous chorioretinopathy

Yong Chai[1,2], Rong-Qiang Liu[1,3], Jing-Lin Yi[2], Ling-Hong Ye[1], Jing Zou[2], Nan Jiang[1], Yi Shao[1]

[1]Department of Ophthalmology, the First Affiliated Hosptal of Nanchang University, Jiangxi Province Clinical Ophthalmology Institute, Nanchang 330006, Jiangxi Province, China

[2]Affiliated Eye Hospital of Nanchang University, Nanchang 330006, Jiangxi Province, China

[3]Postgraduate College, the Third hospital Affiliated of Sun Yat-sen University, Guangzhou 510000, Guangdong Province, China

Co-first authors: Yong Chai and Rong-Qiang Liu

Correspondence to: Yi Shao. Department of Ophthalmology, the First Affiliated Hospital of Nanchang University, Nanchang 330006, Jiangxi Province, China. Freebee99@163.com

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Abstract

• AIM: To compare the effectiveness of combined fenofibrate and spironolactone with fenofibrate alone for treatment of central serous chorioretinopathy (CSCR).

• METHODS: Totally 60 patients (60 eyes) with a history of acute CSCR were randomed into two groups: group A with combination of fenofibrate (200 mg) and spironolactone (100 mg), and group B with only fenofibrate (200 mg). They were taken half an hour before meals and once per day for 8wk. The changes of the visual acuity, subjective symptom, ocular surface disease index (OSDI), the tear film and optical coherence tomography were observed at 2, 4, 6, and 8wk before and after treatment.

• RESULTS: The best corrected visual acuity (BCVA, logMAR) was improved to 0.22 and 0.27 after treatment from baseline of 0.35 and 0.36 in groups A and B (P< 0.05), respectively. After 8wk treatment, the central subfield thickness (CST), and subretinal fluid volumn (SFV) decreased significantly to 49.5% and 78.8% in group A, 37.0% and 57.2% in group B. There were significant differences of CST and SFV in both groups (all P<0.05).

• CONCLUSION: Fenofibrate combined with spironolactone may have more clinical efficacy in the treatment of CSCR than fenofibrate only.

• KEYWORDS: fenofibrate; spironolactone; central serous chorioretinopathy; vision; optical coherence tomography

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INTRODUCTION

Central serous chorioretinopathy (CSCR) is a vision-threatening disease characterized by serous subretinal fluid (SRF) accumulation causing a localized area of retinal detachment[1]. Von Gräfe (1866) first reported this pathology with common clinical symptoms, such as visual distortion, narrowing, floating shadows, and vision loss. The incidence of this disorder continues to increase. CSCR affects about 1 in 10 000 people, with men affected more commonly than women [2-3]. It possesses a long course, a severe symptom and has been a key issue in recent research. The high spontaneous remission rate favors conservative management, lifestyle counseling, and discontinuation of glucocorticoid medication as first-line therapeutic options. Unfortunately, many cases of acute CSCR are not eligible or do not respond to treatment with thermal laser or photodynamic therapy[4].

Fenofibrate could interfere with the multiple mechanisms of CSCR, such as reducing plasma lipids [5], improving endothelial function, inhibiting excessive expression of inflammatory factors [6], reducing apoptosis in the retina [7], and inhibiting the formation of vascular endothelial growth factor (VEGF)[8]. Spironolactone is a synthesis of aldosterone receptor antagonist, which was effective in inhibiting platelet aggregation and the formation of new vessels[9]. To define the effectiveness of this new treatment strategy, we performed a study comparing the results obtained in patients treated with fenofibrate and spironolactone with those in a historic control group consisting of patients with CSCR who were only taking fenofibrate.

SUBJECTS AND METHODS

Subjects and Study Design This was a prospective, randomized comparative study. Patients with symptomatic CSCR of less than a 3-month duration were prospectively recruited between August 2011 and August 2014. A case history and complete ocular surface examination were performed to determine participant eligibility. Sixty patients with acute CSCR were recruited from the Ophthalmology Department of the First Affiliated Hospital of Nanchang University Hospital. The patients who were 30 to 58 years

old were randomly divided into two groups. A combination of fenofibrate (200 mg, once daily) and spironolactone (100 mg, 3 times a day) was used in group A, whereas in group B, only fenofibrate were used. Both groups were treated for 8wk. Patients did not have other ocular histories, hologathy histories, or histories of taking anti-hypertensive or anti-depressant medication. Furthermore, none of the patients were pregnant or lactating. The visual acuity and optical coherence tomography [10] [including mean central subfield thickness (CST), mean subretinal fluid volumn (SFV), mean subretinal fluid vertical diameter (SFVD), mean subretinal fluid horizontal diameter (SFHD)] were conducted at 2, 4, 6, 8wk before and after treatment, respectively. The sample size was set at 30 based on the equation n =15.6R+1.6 under 80% confidence.

Ethical Considerations The study was conducted in accordance with the principles of the Declaration of Helsinki. For each patient, the study protocol and procedure were fully explained, and consent was obtained, according to the Ethics Committee of our hospital.

Recruitment Criteria For all patients, diagnosis was based on the best corrected visual acuity (BCVA), routine eye examination, and fundus fluorescein angiography (FFA) examination[11]. In accordance with CSCR diagnostic criteria, clinical presentation of the disease included: 1) clinical manifestations of visual impairment, floating shadows or central scotoma (blind spot), visual darkening, discoloration, deformation, narrowing, *etc*; 2) FFA examination showing macular edema or discoid anti-halo, with or without yellow/white punctiform exudation or old exudative spots; 3) FFA examination showing either the typical or atypical punctate pigment epithelial leakage on the posterior pole and smoke-like or ink-like stains on the macular area.

Exclusion Criteria Exclusion criteria: 1) history of allergies, trauma, or surgery on eye or kidney; 2) previous diagnosis of eye diseases, such as keratopathy, diabetic retinopathy, previous retinal vein occlusion affecting the retina, diabetic macular edema, exudative age-related macular degeneration, or a history of uveitis within the study eye; 3) previous diagnosis of severe primary disease, such as cardiovascular disease or mental illness; 4) current state of pregnancy, lactation, abnormalities of liver function; 5) any subject unwilling to give informed consent.

Observation Criteria All cases were confirmed by systemic eye tests, fundus imaging, FFA examination, and optical coherence tomography (OCT) examination. The vision tests, FFA, and OCT examinations were performed and compared in patients before treatment and up to 8wk after treatment. Safety indicators included blood pressure, blood lipids, routine laboratory tests on urine and feces, heart examination, and liver examination.

Evaluation Criteria According to standards set by the international standard vision chart, visual acuity >0.1 and improvement in corrected visual acuity by 2 or more were considered to represent an improvement in visual acuity; reduction in visual acuity by 2 or more was regarded to represent a reduction in visual acuity; all other changes in visual acuity represented unchanged visual acuity. Vision therapies causing both improved and unchanged visual acuity were considered to be effective[12].

The criteria for cure assessed through OCT and FFA examinations were as follows: 1) fluorescein leakage from the lesion area was diminished or eliminated; 2) detachment of the lesion area of the neurosensory retina was reduced; 3) visual acuity was improved (more than five alphanumeric codes were increased on ETDRS visual acuity); 4) visual distortion, darkening, and other symptoms were alleviated or diminished completely. Both cure and improvement in symptoms were considered to be therapeutically effective.

The criteria for alleviation of symptoms assessed through OCT and FFA examinations were as follows: 1) fluorescein leakage from the lesion area was diminished or eliminated; 2) detachment of the lesion area of the neurosensory retina was reduced; 3) visual distortion, darkening and other symptoms were alleviated; 4) visual acuity remained unchanged (less than five alphanumeric codes were increased or decreased on ETDRS visual acuity) or improved (five alphanumeric codes were increased on ETDRS visual acuity).

The criteria for ineffective treatment assessed through OCT and FFA examinations were as follows [13]: 1) fluorescein leakage from the lesion area deteriorated or improved insignificantly; 2) detachment of the lesion area of the neurosensory retina remained unchanged or had worsened; 3) visual acuity was reduced (more than five alphanumeric codes were decreased on ETDRS visual acuity); 4) visual distortion, darkening, and other symptoms remained unchanged or had worsened

Termination of Observations The criteria for termination of observations were as follows: 1) medication was stopped when alanine aminotransferase increased to >80 U/L during medication and muscle pain and/or muscle weakness occurred; 2) the symptoms worsened during treatment, resulting in the patient requiring immediate laser treatment; 3) the patient showed high blood pressure or acute cardiovascular disease; 4) CSCR led to vitreous hemorrhage, retinal detachment, and/or other circumstances that required vitrectomy combined with intraocular laser surgery.

Statistical Analysis All values are expressed as means ± standard deviation (SD). ANOVA was used for all indexes before and after treatment comparisons; Dunnett's test was applied for multiple comparisons. Differences between two groups were performed using the paired t-test. A value of P<0.05 was considered statistically significant. Calculations and statistical analyses were performed using the 19.0 software package for Windows (SPSS, China).

Table 1 Characteristics of included patients in the study $\bar{x} \pm s$

Variables	Group A	Group B	t	P
Age (range, a)	50.78±10.26 (32-55)	51.19±11.76 (30-58)	0.356	0.724
Sex (M/F)	24/6	25/5	0.752	0.992
Laterality (right/left)	16/14	17/13	0.534	0.492
Spherical equivalent refractive error (diopters)	-1.78±2.35 (-3.75-2.5)	-1.86±2.25 (-3.5-3.75)	0.032	0.663
Duration of CSCR (d)	3.57±4.19 (1-9)	3.57±3.88 (1-11)	0.683	0.562
No. of eyes with PED (%)	3 (10.0%)	4 (13.3%)	0.935	0.329
FBG (mmol/L)	5.78±2.57	5.89±2.51	0.848	0.821
BMI	26.43±4.12	23.84±5.21	0.825	0.832
Smoking status no./total no. (%)				
Nerver smoked	12 (40)	11 (36.7)	0.011	0.682
Former smoker	9 (30)	11 (36.7)	0.021	0.493
Current smoker	9 (30)	8 (26.6)	0.013	0.575

CSCR: Central serous chorioretinopathy; PED: Pigment epithelium detachment; FBG: Fasting blood glucose; BMI: Body mass index.

RESULTS

Baseline Characteristics The average patient age was 51, ranging from 30 to 58y and the average baseline BCVA (logMAR) was 0.1 to 0.48. There were no significant difference in the age, the sex, axial length between two groups (all P>0.05). The details are presented in Table 1.

Best Corrected Visual Acuity Follow-up time was divided into several periods and plotted using a mixed model analysis. Since time on drugs ranged from 1 to 14d, 2-week divisions were chosen as the timeframe to avoid multiple visits in one period for each observation; thus, follow-up time was divided into baseline visit (before treatment), 0-2wk, 2-4wk, 4-6wk, and 6-8wk.

In group A (fenofibrate and spironolactone), the average baseline BCVA was 0.35 logMAR (range: 0.16-0.48 logMAR) and the average BCVA was 0.22 logMAR (range 0.10-0.46 logMAR) at study completion. The decrease was statistically significant at the fourth follow-up period (6-8wk after treatment) compared with baseline (P=0.02). In group B (fenofibrate alone), the average baseline BCVA was 0.36 logMAR (range: 0.14-0.49 logMAR) and the average BCVA was 0.27 logMAR (range 0.12-0.46 logMAR) at study completion. The decrease was statistically significant at the fourth follow-up period (6-8wk after treatment) compared with baseline (P=0.02). During the follow-up, the visual acuities of 50 eyes were improved or unchanged (group A: 28 eyes; group B: 22 eyes); the differences in improved BCVA between the two groups before and after treatment were statistically significant (P<0.05, Figure 1).

Optical Coherence Tomography Analysis In group A, the average baseline CST was 341.5 μm (range: 320.21 to 374.39 μm) and the baseline SFV was 0.99 μm (rang: 0.52 to 1.67 μm). The average baseline SFVD was 138.25 μm (range: 110.54 to 164.94 μm) and the baseline SFHD was 2386.24 μm (rang: 1920.35 to 2652.73 μm). At study completion, average CST was 172.54 μm (range: 109.54-221.82 μm) and the baseline SFV was 0.21 μm (rang: 0.08 to 0.39 μm). The average SFVD was 28.63 μm (range: 11.21 to 68.55 μm) and the SFHD was 226.17 μm (rang: 106.36 to 368.25 μm). The CST, SFV, SFVD and SFHD significantly decreased significantly (49.5%, 78.8%, 79.3%, 90.5% , respectively), and the decrease was statistically significant at the fourth follow-up (6-8wk after treatment) compared with the baseline (P=0.032, 0.019, 0.028, and 0.012, respectively). In group A, 20 eyes (66.7%) within the study demonstrated complete resolution of SFV at treatment completion, which ranged from 1 to 8wk as time of resolution. Two eyes (6.7%) demonstrated no treatment effect throughout treatment duration.

In group B (fenofibrate alone), the average baseline CST was 343.75 μm (range: 312.32 to 378.53 μm) and baseline SFV was 0.98 μm (range: 0.55 to 1.59 μm). The average baseline SFVD was 136.89 μm (range: 113.27 to 160.47 μm) and baseline SFHD was 2294.82 μm (range: 1916.37 to 2654.62 μm). At study completion, average CST was 216.54 μm (range: 134.46 to 234.78 μm) and baseline SFV was 0.42 μm (range: 0.16 to 0.71 μm). The average SFVD was 56.36 μm (range: 36.25 to 100.71 μm) and SFHD was 619.39 μm (range: 521.84 to 768.16 μm). The CST, SFV, SFVD and SFHD decreased significantly (37.0%, 57.2%, 58.8%, 73.0%, respectively), and the decrease was statistically significant at the fourth follow-up period (6-8wk after treatment) compared with baseline (P=0.044, 0.032, 0.046, and 0.019, respectively). In group B, 12 eyes (40%) within the study demonstrated complete resolution of SFV at treatment completion, which ranged from 1 to 8wk as time of resolution. Eight eyes (26.7%) demonstrated no treatment effect throughout the duration of treatment. Eight eyes (26.7%) improved but had incomplete resolution after treatment, while two eyes (6.7%) exhibited worsened SFV on OCT. There were statistically

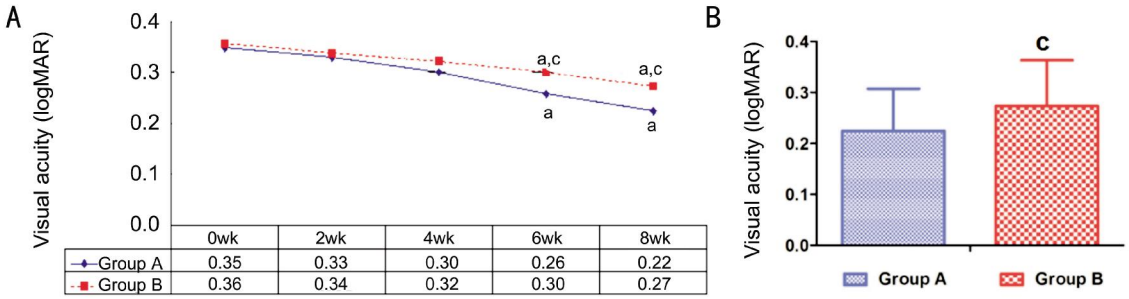

Figure 1 Time course of the mean best corrected visual acuity of eyes with acute central serious chorioretinopathy that underwent drugs treatment in both groups A: The Time course of the mean BCVA in each group at 2, 4, 6, and 8wk after treatment. The BCVA is significantly better at 8wk than at baseline in both groups. B: Analysis of the BCVA in the two groups at 8wk after treatment. Data are shown as mean±SD. n =30; Before therapy *vs* after therapy, $^aP < 0.05$; Group A *vs* Group B, $^cP < 0.05$.

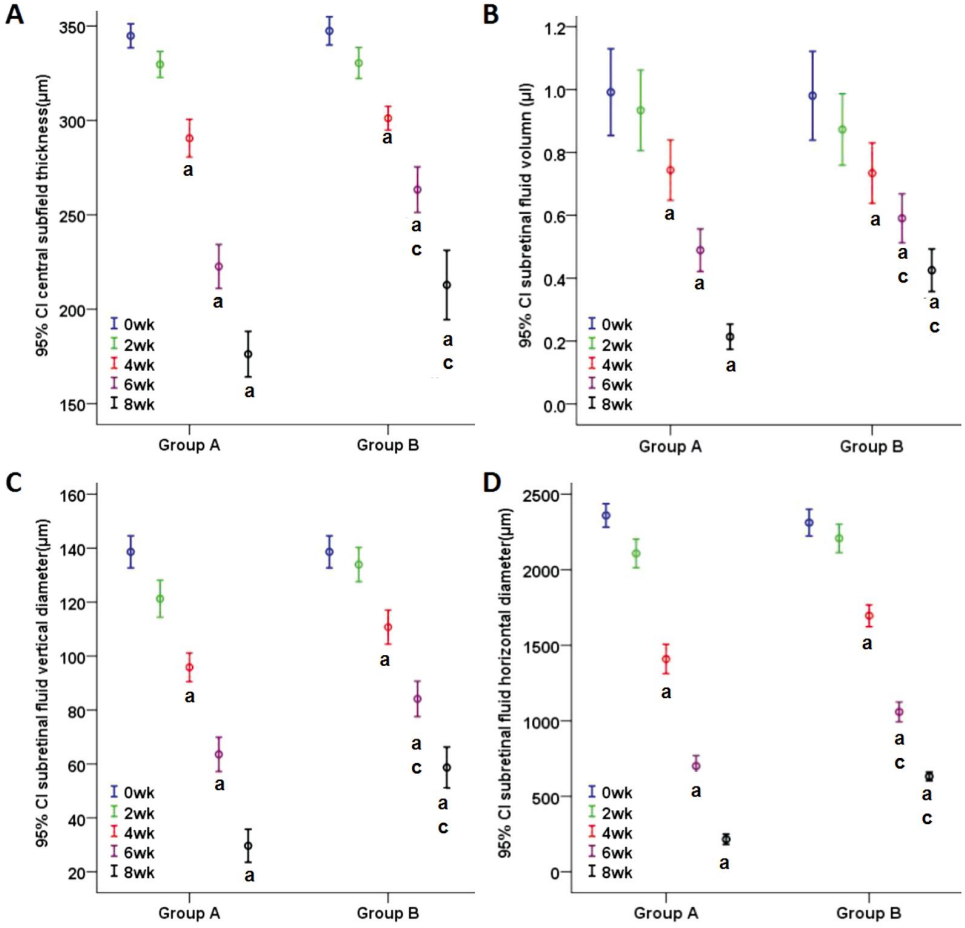

Figure 2 Alterations in macular area by optical coherence tomography The trend of subretinal fluid reduction measured by OCT at baseline and follow up visits at 2, 4, 6 and 8wk after the onset of treatment. Mean central subfield thickness (μm) (A), mean subretinal fluid volumn (μL) (B), mean subretinal fluid vertical diameter (μm) (C), mean subretinal fluid horizontal diameter (μm) (D) were declined at 8wk. The sample size was 30 cases for group A and 30 cases for group B throughout the study. Before therapy *vs* after therapy, $^aP < 0.05$; Group A *vs* Group B, $^cP < 0.05$.

significant differences for CST, SFV, SFVD and SFHD at the fourth follow-up period in both groups (all P<0.05). Figure 2 demonstrates the alterations in macular area in both groups using OCT.

Clinical Safety and Validity Compared with before therapy, the item [including glutamic-pyruvic transaminase (GPT), glutamic-oxalacetic transaminase (GOT), urine creatinine (UCr), blood urea nitrogen (BUN)] had no obvious change at 8wk after therapy in both groups (all P >0.05, Table 2). Totally 8wk after treatment, the difference between two drugs for systolic blood pressure (SBP) and diastolic blood pressure (DBP) was statistically significant, whereas the difference of blood lipid [including triglyceride (TG) and total cholesterol (TC)] was not statistically significant (all P>0.05), as shown in Table 2.

After 8wk treatment, the cure rate of group B was 46.7%, total effective rate was 73.3%, while the cure rate of group A was 66.7%, total effective rate was 93.3%, there was statistical difference in total effective rate between two groups (χ^2=19.184, P< 0.05), as shown in Table 3.

Table 2 The clinical safety in both groups before and after therapy

Variables	Group A		Group B		*t*	*P*
	Before	After	Before	After		
GPT (μmol/L)	22.16±7.88	24.86±6.42	24.05±5.74	23.53±6.62	0.138	0.812
GOT (μmol/L)	30.19±6.74	28.85±5.16	29.17±6.86	31.86±6.46	0.869	0.554
SBP (mm Hg)	132.45±17.51	112.53±16.32[a]	134.56±156.98	126.28±24.16[c]	7.614	0.006
DBP (mm Hg)	86.35±11.34	72.26±5.67[a]	87.38±9.43	82.91±12.19[c]	10.527	0.024
TG (mmol/L)	1.12±0.32	0.69±0.23[a]	1.18±0.37	0.79±0.21[a]	0.418	0.639
TC (mmol/L)	4.88±1.54	3.12±1.15[a]	4.95±1.32	3.09±1.18[a]	0.681	0.421
UCr (μmol/L)	62.21±18.09	59.26±14.95	63.71±19.51	64.53±14.53	0.774	0.096
BUN (μmol/L)	3.76±0.93	3.82±0.68	3.71±0.99	3.66±0.57	1.952	0.322

Before therapy *vs* after therapy, [a]$P<0.05$; Group A *vs* Group B, [c]$P<0.05$. GPT: Glutamate pyruvic transaminase; GOT: Glutamate oxaloacetate transaminase; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TG: Triglyceride; TC: Total cholesterol; UCr: Urine creatinine; BUN: Blood urea nitrogen.

Table 3 The relationship between age, gender, history and therapeutic in both groups (eyes)

Variables (A/B)	Eyes	Curation	Amelioration	Aggravation	χ^2	*P*
Age (a)						
＜50	12/16	6/6	5/6	1/4	3.126	0.026
≥50	18/14	14/8	3/2	1/4	5.092	0.008
Gender						
M	24/25	18/12	5/6	1/7	4.683	0.045
F	6/5	2/3	3/2	1/1	2.159	0.072
Laterality						
Left	16/17	10/6	5/7	1/4	4.683	0.045
Right	14/13	10/8	3/1	1/4	2.159	0.072
History (d)						
＜5	14/16	9/8	4/4	1/4	2.683	0.038
≥5	16/14	11/6	4/4	1/4	7.339	0.017
Total	30/30	20/14	8/8	2/8	19.184	0.006

DISCUSSION

Typical acute CSCR is characterized by duration of symptoms and/or retinal detachment of less than 6mo and monofocal or paucifocal fluorescein angiographic retinal pigment epithelium (RPE) leakage[14]. Without early treatment, long-term macular edema would damage visual function in some patients, which ultimately leads to degeneration of visual cells. That has not yet fully understood, but various studies have shown that it might be associated with corticosteroids, drinking, or decreased function of the immune system. While it is true that exact cause of CSCR the duration of detachment, the mechanism by which this is achieved remains controversial. Spitznas [15] has reviewed the experimental evidence on the nature of the RPE abnormality, which postulated a reversal in the direction of water transport across the abnormal RPE-such that this occurs from the choroid towards the neuroretina. In addition, elevated serum cholesterol leads to macular edema and hard exudation, which is associated with the development and severity of CSCR. More specifically, an elevation in triglycerides is associated with macular edema and hard exudation. Blood circulation drugs and glucocorticoid antagonist have been the traditional treatment for this disease. However, this type of drugs has the potential to worsen symptoms, cause interlayer effusion, recurrence, and/or visual distortion for patients with retinal macular edema. This poses a serious threat to visual acuity. Laser photocoagulation treatment only closes the RPE leakage by laser thermal effects, but does not reduce the abnormal choroidal blood flow, however, PDT treatment could decrease choroidal thickness by reducing the abnormal choroidal blood flow[16]. They also have the potential to elicit non-selective coagulation necrosis on the adjacent tissue of lesion area, which would result in several adverse effects, such as the formation of central scotoma, the reduction of contrast sensitivity, and secondary choroidal neovascularization. Intravitreal anti-VEGF therapy has been demonstrated with profitable results in several chronic CSCR [17-20]. Nevertheless, large-scale multicenter clinical controlled trials are necessary to evaluate the efficacy and safety of anti-VEGF therapy for CSCR. In addition, virectomy is ineffective for CSCR. Thus, furthering the understanding of the mechanism of angiogenesis, making

breakthroughs on possible treatments, and discovering new drugs and key therapeutic targets to prevent CSCR have become the focus of the current ophthalmic research.

Fenofibrate is the third generation phenoxy aromatic acid derivative tune pharmaceuticals and has several functions, such as activating PPARα, reducing ApoC-III mRNA expression in the liver, decreasing the plasma ApoC-III, stimulating the expression of ApoAI genes, improving the lipoprotein lipase activity in adipose tissue, and accelerating the catabolism of TG-rich lipoprotein. Fenofibrate also improves the progression of diabetic retinopathy and promotes the absorption of macular edema through non-lipid mediation effects. Recent large-scale clinical studies, including the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) and Action to Control Cardiovascular Risk in Diabetes (ACCORD) studies, examined the effects of fenofibrate on cardiovascular risk and diabetes complications in type 2 diabetes [21-22]. Taking 200 mg of fenofibrate daily failed to affect visual acuity measures, but could significantly decrease the need for using laser treatment in patients with diabetic macular edema and proliferative retinopathy, and it promotes 30% of the absorption of macular edema [23]. These findings have resulted in recommendations that fenofibrate be used as an adjunct treatment for type 2 diabetic patients with nonproliferative diabetic retinopathy[24-25].

As we know, glucocorticoids is associated with CSCR and glucocorticoids shows to some extent an affinity for the mineralocorticoid receptor (MR). It has been proposed that excessive glucocorticoid-dependent choroidal MR activation in choroid vessels may be involved in the pathogenesis of CSCR [26]. Zhao *et al* [27] have observed in rat studies that intravitreous injection of a specific MR activator aldosterone, induced dilation of choroidal vessels and leakage. Similar observations have been confirmed on human Müller glial cell lines [28]. MR is expressed in neuroretina and choroid; excessive MR activation may promote vascular oxidative stress and inhibit vascular relaxation. Subsequently, it may contribute to vessel inflammation, fibrosis and remodeling, and lead to choroidal and retinal neovascularization. Spironolactone as a strong MR antagonists, can inhibit the formation of new blood vessels [29-30], inhibition of platelet aggregation, vascular endothelial function to recover leakage of the choroidal vasculature and decrease choroidal thickness. The use of MR drugs such as spironolactone has been considered as a treatment option for patients with CSCR.

We previously reported that fenofibrate acts as an efficacy medicine in patients with CSCR. This study found that the proper use of fenofibrate presents the capability to delay the development process of acute CSCR. After 8wk, CST, SFV, SFVD and SFHD values were less after treatment than before treatment in group B (P<0.05), and the levels were even lower compared with group A (P<0.05). That fenofibrate alone is by no means to prevent vascular endothelial injury and significantly improves blood hypercoagulable state. Spironolactone has inhibiting new blood vessels, improving vascular endothelial function. Therefore, we combined fenofibrate with spironolactone in treating acute CSCR. This study shows that combined (group A) not only significantly reduces the CST, but also reduces SFV and improves BCVA significantly superior to fenofibrate alone (group B). After combination therapy CST, SFV, SFVD, SFHD of group A compared with before treatment were significantly lower (P<0.05).

The purpose of this study was to examine the effectiveness of spironolactone and fenofibrate, as a treatment option for acute CSCR. The goal of spironolactone treatment for acute CSCR was to reduce and resolve foveal SFV while improving visual outcomes. Following therapy, there was a significant reduction in CST, SFV, SFVD, SFHD and improved visual acuity in eyes with acute CSCR. No adverse events were found to be associated with the treatment. Our study also has limitations, including the small number of patients only the type with acute CSCR and the short follow-up period. Further studies will be needed to be able to individualize the recurrence or long-term effects of this multifactorial illness.

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