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Original Article

Clinical findings associated with propranolol and fenofibrate on acute central serous chorioretinopathy

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Abstract: Objective: To evaluate the effects of fenofibrate with propranolol in the pathophysiology of acute central serous chorioretinopathy (CSCR). Methods: Totally 48 patients (48 eyes) with a history of acute CSCR were randomed divided into two groups: group A was treated with a combination of fenofibrate (200 mg) and propranolol (60 mg, 3 times daily) for 8 weeks, and group B with only fenofibrate (200 mg, once daily). The visual acuity, subjective symptom, OSDI, tear film test with 4 terms, tear protein and optical coherence tomography [including mean central subfield thickness (CST), mean subretinal fluid volumn (SFV), mean subretinal fluid vertical diameter (SFVD) and mean subretinal fluid horizontal diameter (SFHD)] were observed at every other week before and after treatment. Results: After treatment, the average baseline BCVA was 0.35 logMAR for group A and 0.36 logMAR for group B, respectively. And the average BCVA was 0.21 logMAR and 0.27 logMAR, for each group respectively. The differences of improved BCVA before and after treatment between the two groups were statistically significant ($P<0.05$). In group A, the average CST was 181.54 μm and baseline SFV was 0.17 μm. The average SFVD was 28.63 μm and SFHD was 203.83 μm. The decrease of CST, SFV, SFVD and SFHD was statistically significant at the fourth follow-up (6-8 weeks after treatment) compared with baseline ($P=0.021$, 0.018, 0.029, and 0.017, respectively). In group B, the average CST was 226.88 μm and baseline SFV was 0.40 μm. The average SFVD was 56.54 μm and SFHD was 654.54 μm. These parameters were also statistically significantly decreased at the fourth follow-up period (6-8 weeks after treatment) compared with baseline ($P=0.041$, 0.025, 0.033, and 0.011, respectively). We also observed significant differences between these two groups for the CST, SFV, SFVD and SFHD at the fourth follow-up (all $P<0.05$). Conclusion: Fenofibrate combined with propranolol is more clinically efficient than fenofibrate only in the treatment of patients with CSCR.

Keywords: Fenofibrate, propranolol, CSCR, vision, OCT

Introduction

Central serous chorioretinopathy (CSCR) is a vision-threatening disease characterized by serous subretinal fluid (SRF) accumulation causing localized retinal detachment. Although it is usually self-limiting, CSCR may recur chronically with permanent impairment of visual acuity [1]. CSCR affects men more commonly than women [2, 3]. It is a long-term disease with severe symptoms and has been a key issue in recent research. Previously recommended treatments for non-resolving or recurrent CSCR include invasive techniques, such as laser photocoagulation and photodynamic therapy. Unfortunately, many cases of acute CSCR are not eligible or do not respond to treatment with thermal laser or photodynamic therapy.

Fenofibrate could alleviate CSCR symptons under multiple mechanisms, such as reducing plasma lipids [4], improving endothelial function, inhibiting excessive expression of inflammatory factors [5], reducing apoptosis in the retina [6], and inhibiting the formation of vascular endothelial growth factor (VEGF) [7]. Beta-adrenoceptor antagonists have been suggested as an alternative treatment. Although their usage in patients have been reported, combination with propranolol has never been explored. CSCR has been associated with physiological changes, including elevated blood pr-

essure and raised serum cortisol and epinephrine [8]. Propranolol is a beta-adrenoceptor antagonist, effective in reducing platelet adhesion and aggregation [9]. We previously reported that fenofibrate acts as an efficacious medicine in patients with CSCR [10]. In this study, we evaluated the effects of propranolol combining with fenofibrate in the pathophysiology of CSCR and the role of beta-blockade in treating this condition.

Materials and methods

Patients and study design

This was a prospective randomized comparative study. Symptomatic CSCR patients with less than a 3-month duration were recruited between August 2011 and August 2015 from the Ophthalmology Department of the First Affiliated Hospital of Nanchang University hospital. To determine participant eligibility, complete ocular surface examination was performed and case history was analyzed. Sixty patients with acute CSCR were recruited. Patients did not have histories of other ocular medication, hologathy, anti-hypertensive or antidepressant medication. Furthermore, none of the patients were pregnant or lactating. The patients aged from 25 to 51 years old were randomly divided into two groups. A combination of fenofibrate (200 mg, 1 time a day) and propranolol (20 mg, 3 times a day) was used in group A, while group B were treated with fenofibrate only. Treatment length for both groups was 8 weeks. Ocular paremeters including visual acuity and optical coherence tomography [11] [including mean central subfield thickness (CST), mean subretinal fluid volumn (SFV), mean subretinal fluid vertical diameter (SFVD), mean subretinal fluid horizontal diameter (SFHD)] were measured at 2, 4, 6, 8 weeks before and after treatment, respectively. Based on the equation n=15.6R+1.6 under 80% confidence, the sample size was set at 24.

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, 'best correct visual acuity' (BCVA), routine eye examination, and fundus fluorescein angiography (FFA) examination were performed [11]. According to the CSCR diagnostic criteria, clinical manifestations include: (1) visual impairment, visual darkening, narrowing, deformation, discoloration, floating shadows or central scotoma (blind spot) *etc*.; (2) macular edema or discoid anti-halo, with or without yellow/white punctiform exudation or old exudative spots; (3) typical or atypical punctate pigment epithelial leakage on the posterior pole and smoke-like or ink-like stains on the macular area in the FFA examination.

Exclusion criteria

Subjects with following conditions were excluded: a history of retinal vascular diseases including diabetic retinopathy, retinal vein occlusion, diabetic macular edema, exudative age-related macular degeneration (AMD), or a history of uveitis in the study eye. Other exclusion criteria included: (1) other ocular diseases, such as keratopathy; (2) other severe primary diseases, such as cardiovascular disease or mental illness, abnormalities of liver functions; (3) a history of allergies, trauma, or surgery on the eye or kidney; (4) pregnancy and lactation; (5) previous history of CSCR treatment.

Observation criteria

All patients were analyzed with systemic eye tests, fundus imaging, FFA examination, and OCT examination and the results were compared before treatment and up to 8 weeks after treatment. Safety indicators were carefully monitored, which included blood pressure, blood lipids, routine laboratory tests on urine and feces, hear examination, and liver examination.

Evaluation criteria

According to the international standard vision chart, a change in visual acuity was considered as visual acuity >0.1 and improvement/reduction in corrected visual acuity by 2 or more; all other changes in visual acuity were considered unchanged visual acuity. Vision therapies causing both improved and unchanged visual acuity were considered to be effective [12].

Table 1. Characteristics of included participants in the study

Variables	A	B	t	p
Age (Range, years)	43.14±10.26 (25-51)	41.64±11.35 (24-50)	0.412	0.753
Sex (Male to female)	20/4	21/3	/	1
Laterality (right:left)	16/8	14/10	0.356	0.551
Spherical equivalent refractive error (diopters)				
Mean ± SD (Range)	-1.60±2.25 (-3.5-2.75)	-1.75±2.15 (-3.75-3.50)	0.042	0.754
Duration of CSCR (days)	7.24±4.15 (1-14)	7.89±5.14 (1-12)	0.831	0.725
Number of eyes with PED (%)	3 (12.5%)	2 (8.3%)	0.912	0.721
Fbg (mmol/L)	5.64±1.92	5.79±1.52	0.814	0.745
SC (mmol/L)	67.16±11.43	63.12±13.94	0.723	0.652
BMI	23.98±4.51	24.31±3.63	0.827	0.442
Smoking stutus no./total no. (%)				
Nerver Smoked	10 (41.7)	8 (33.3)		
Former Smoker	6 (25)	8 (33.3)	0.508	0.776
Current Smoker	8 (33.3)	8 (33.3)		

Abbreviations: PED, pigment epithelium detachment; SD, standard deviation. BCVA, best corrected visual acuity.

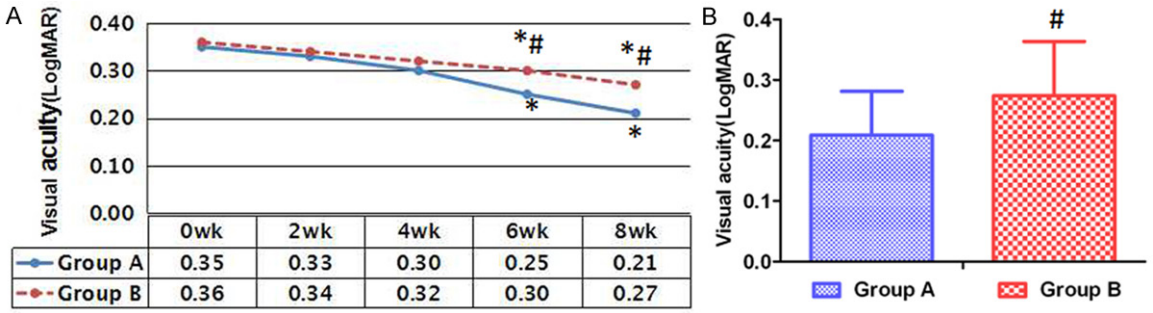

Figure 1. Time course of the mean best corrected visual acuity of eyes with acute central serious chorioretinopathy that underwent drugs treatment in both groups. A: The Time course of the mean BCVA in each group at 2, 4, 6, and 8 weeks after treatment. The best corrected visual acuity is significantly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

Termination of observations

The observations were terminated if (1) medication was stopped due to an increase of alanine aminotransferase to >80 U/L during medication and muscle pain and/or muscle weakness; (2) the symptoms were aggravated during treatment, leading to immediate laser treatment; (3) high blood pressure or acute cardiovascular disease in the patients; (4) CSCR caused retinal detachment, and/or other circumstances that require vitrectomy combined with intraocular laser surgery.

Statistical analyses

All values are expressed as means ± standard deviation (SD). ANOVA analysis was used for all indexes to compare before and after treatment, and multiple comparisons were performed with the Dunnett's-test. Differences between two groups were compared using the paired t-test. $P<0.05$ was considered statistically significant. All statistical analyses were performed using the 19.0 software package for Windows (SPSS, China).

Results

Baseline characteristics

The average age was 43 (ranging from 24 to 51 years) and the average baseline BCVA (logMAR) was 0.1 to 0.50. There were no significant differences in the age, sex, axial length between

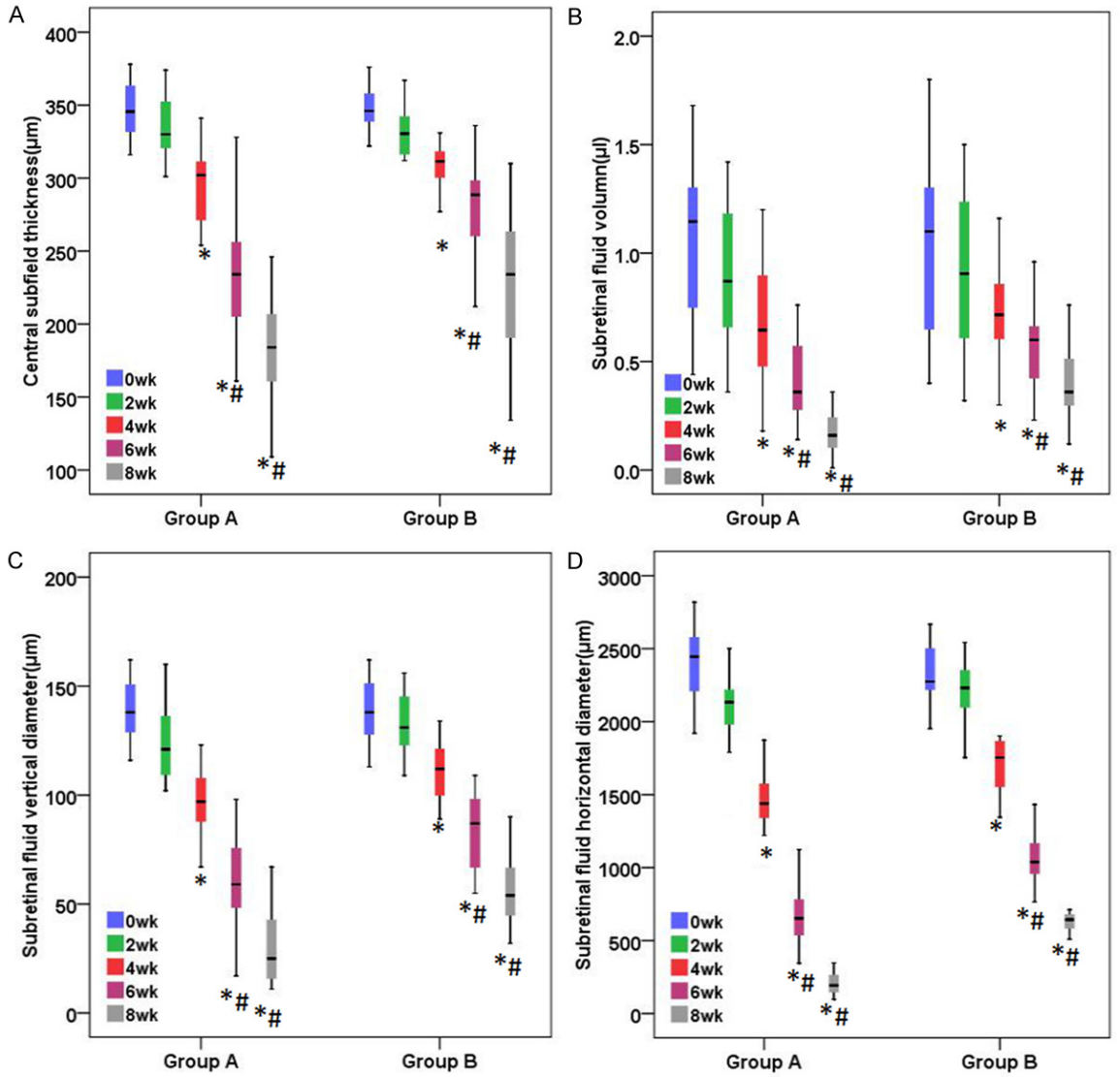

Figure 2. Alterations in the macular area as measured with the optical coherence tomography. Compared to the baseline, subretinal fluid showed reduction at 2, 4, 6 and 8 weeks after treatment. Mean central subfield thickness (μm) (A), mean subretinal fluid volumn (μl) (B), mean subretinal fluid vertical diameter (μm) (C), mean subretinal fluid horizontal diameter (μm) (D) were decreased at 8 weeks. The sample size was 24 throughout the study. Before therapy *vs* after therapy, *P<0.05; group A *vs* group B, #P<0.05.

two groups (all P>0.05). The details are presented in **Table 1**.

The best corrected visual acuity (BCVA)

In the group A with fenofibrate and propranolol treatment, the average baseline BCVA and the average BCVA were 0.35 logMAR (range: 0.16-0.48 logMAR) and 0.21 logMAR (range 0.10-0.42 logMAR) at end of the study, respectively. There was statistically significant reduction at the fourth follow-up period (6-8 weeks after treatment) compared with baseline (P=0.018). In the group B treated with fenofibrate alone, the average baseline BCVA and the average BCVA were 0.36 logMAR (range: 0.14-0.49 logMAR) and 0.27 logMAR (range 0.10-0.48 logMAR) at end of the study, respectively. Similarily, we observed statistically significant decrease at the fourth follow-up period (6-8 weeks after treatment) compared with baseline (P=0.024). During the follow-up, 20 eyes in group A and 14 eyes in group B showed improved or unchanged visual acuities, and the differences in improved BCVA between the two groups were statistically significant both before and after treatment (P<0.05, **Figure 1**).

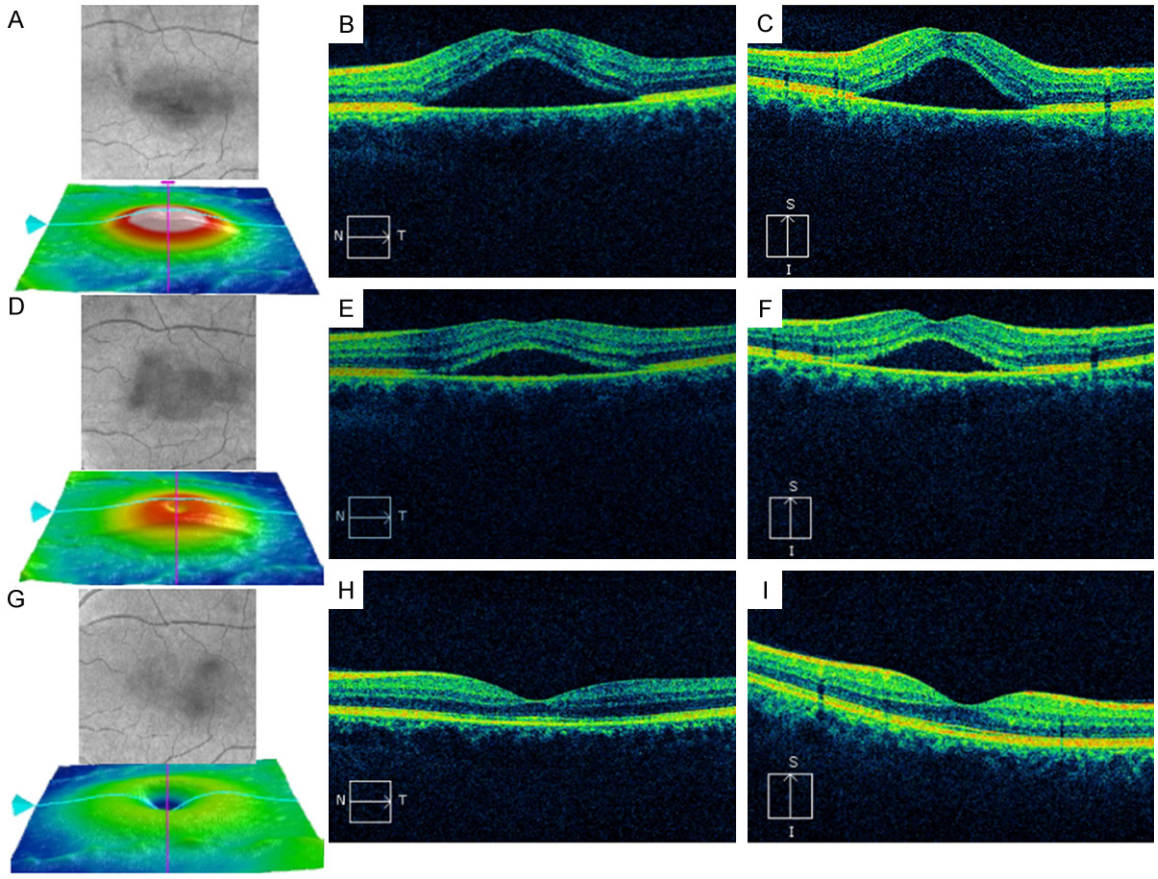

Figure 3. OCT images generated using the Cirrus HD-OCT 4000 (Zeiss, Germany) in an 46-year-old female with CSCR in group A (A-I). The fundus images and topographic maps showed highly bulged swelling macular retinal edema, and loss of the fovea (A). Horizontal scanning (B) and vertical scanning (C) indicated significant retinal detachment. After 4 weeks of treatment with fenofibrate combined with propranolol, fundus images and topographic maps (D), horizontal scanning (E) and vertical scanning (F) showed that the macular retinal swelling was lower than before, the fovea was still disappeared, and the macular retinal detachment was slightly improved. After 8 weeks continuous treatment, fundus images and topographic map (G), horizontal scan (H) and vertical scanning (I) showed that macular edema significantly disappeared, macular spot became clear, macular retinal detachment was improved, and macular retinal structure generally returned to normal.

Optical coherence tomography (OCT) analysis

In the group A, the average baseline CST was 346.71 μm (range: 316.52 to 379.36 μm) and the baseline SFV was 1.07 μm (rang: 0.50 to 1.69 μm). The average baseline SFVD was 139.71 μm (range: 108.76 to 162.63 μm) and the baseline SFHD was 2395.75 μm (rang: 1925.66 to 2342.54 μm). By the end of the study, the average CST was 181.54 μm (range: 107.12-226.69 μm) and the baseline SFV was 0.17 μm (rang: 0.06 to 0.38 μm). The average SFVD was 28.63 μm (range: 11.29 to 69.75 μm) and the SFHD was 203.83 μm (range: 101.77 to 360.29 μm). The ocular parameters including CST, SFV, SFVD and SFHD were significantly decreased at the fourth follow-up (6-8 weeks after treatment) compared with the baseline (P=0.021, 0.018, 0.029, and 0.017, respectively).

In contrast, in the group B, the average baseline CST was 348.75 μm (range: 311.08 to 379.37 μm) and baseline SFV was 1.04 μm (range: 0.51 to 1.53 μm). The average baseline SFVD was 139.54 μm (range: 119.82 to 162.79 μm) and baseline SFHD was 2230.29 μm (range: 1921.54 to 2689.78 μm). By the end of the study, the average CST was 226.88 μm (range: 131.15 to 239.79 μm) and the baseline SFV was 0.40 μm (range: 0.13 to 0.82 μm). The average SFVD was 56.54 μm (range: 36.12 to 102.41 μm) and the SFHD was 654.54 μm (range: 514.86 to 772.91 μm). The ocular

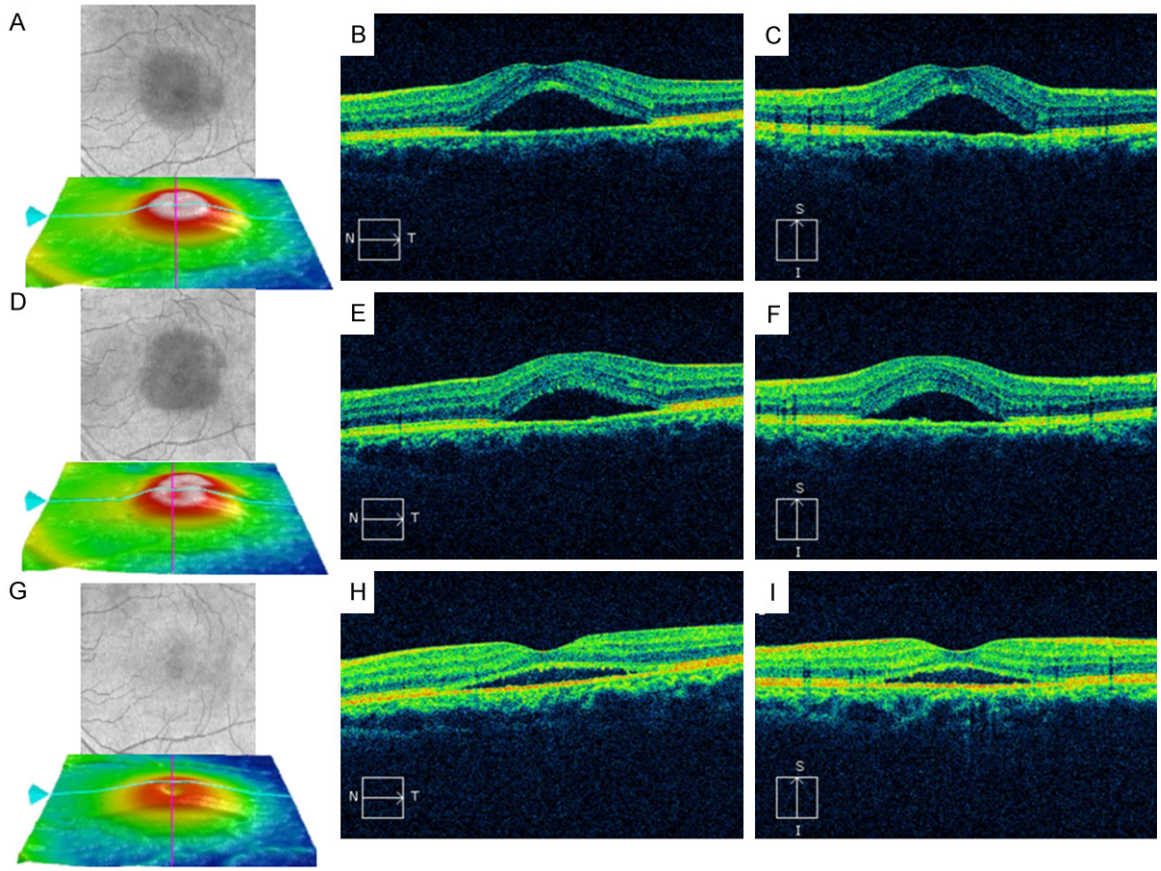

Figure 4. OCT images generated using the Cirrus HD-OCT 4000 (Zeiss, Germany) in a 46-year-old female with CSCR in group B (A-I). The fundus images and topographic maps showed highly bulged swelling macular retinal edema, and loss of the fovea (A). Horizontal scanning (B) and vertical scanning (C) indicated significant retinal detachment. After 4 weeks of treatment with fenofibrate combined with propranolol, fundus images and topographic maps (D), horizontal scanning (E) and vertical scanning (F) showed that the macular retinal swelling was lower than before, the fovea was still disappeared, and the macular retinal detachment was slightly improved. After 8 weeks continuous treatment, fundus images and topographic map (G), horizontal scan (H) and vertical scanning (I) showed that macular edema significantly disappeared, macular spot became clear, macular retinal detachment was improved, and macular retinal structure generally returned to normal.

parameters CST, SFV, SFVD and SFHD were also significantly decreased at the fourth follow-up period (6-8 weeks after treatment) compared with the baseline (P=0.041, 0.025, 0.033, and 0.011, respectively). There were also statistically significant differences for CST, SFV, SFVD and SFHD at the fourth follow-up period between these two groups (all P<0.05). **Figure 2** demonstrates changes in the macular area in both groups using the optical coherence tomography.

Typical cases

In two representative cases of early CSCR in the right eye of middle-aged males, the symptoms and the OCT fundus images and topographic maps were similar (**Figures 3A-C**, **4A-C**). Under the same conditions, case one was treated with fenofibrate combined with propranolol for 4 weeks of continuous regular treatment; and case two was treated with fenofibrate alone for 4 weeks. OCT scanning of follow-up showed that both cases were alleviating symptoms with no significant difference observed between these two cases (**Figures 3D-F**, **4D-F**). After 4 weeks of additional treatment, case one patient was significantly better than case two patient, as observed with OCT scanning. Case one improved to nearly normal, whereas case two also showed significant improvement (**Figures 3G-I**, **4G-I**). Therefore we can conclude that and fenofibrate alone can both alleviate symptoms of early onset CSCR after 4 weeks of

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

Variables	A		B		t	p
	Before	After	Before	After		
GPT (μmol·L^{-1})	23.66±7.39	23.12±5.56	24.09±7.92	24.76±6.12	0.089	0.571
GOT (μmol·L^{-1})	29.76±6.17	87.29±5.83	28.89±7.88	29.72±6.93	0.536	0.814
SDP (mmHg)	131.28±16.92	114.72±15.13*	132.86±18.72	124.66±20.52#	8.541	0.032
DBP (mmHg)	88.55±9.75	71.12±6.57*	89.36±9.69	85.91±12.54#	12.345	0.013
TG (mmol·L^{-1})	1.18±0.32	0.78±0.11*	1.15±0.32	0.81±0.26*	0.361	0.134
TC (mmol·L^{-1})	4.71±1.16	3.07±1.29*	4.78±1.21	3.39±0.68*	0.687	0.213
UCr (μmol·L^{-1})	62.96±18.76	63.26±14.17	64.36±19.54	65.39±14.77	0.916	0.357
BUN (μmol·L^{-1})	3.87±0.77	3.52±0.69	3.79±0.98	3.67±0.54	0.586	0.691

Note: Before therapy *vs* after therapy, *P<0.05; group A *vs* group B, #P<0.05.

treatment, and there are no significant differences between these two regimens. Additional 4 weeks of treatment suggests that fenofibrate combined with propranolol is significant better than fenofibrate alone.

The clinical safety and validity

Compared with baseline before treatment, the safety indices (including GPT, GOT, UCr, BUN) had no obvious change at 8 weeks after treatment in both groups (all P>0.05, **Table 2**). Additionally, after 8 weeks of treatment, there was statistically significant difference between two treatments for SBP and DBP, whereas the difference of blood lipid (including TC and TG) was not statistically significant (all P>0.05), as shown in **Table 2**.

Discussion

Acute CSC is characterized by monofocal or paucifocal fluorescein angiographic retinal pigment epithelium leakage and/or retinal detachment of with a duration less than 6 months [13]. Without early treatment, chronic macular edema would lead to degeneration of retina cells, and ultimately damage visual functions. The causes of the disease are not yet fully understood, but various studies suggest that it might be associated with corticosteroids, alcohol, or immunodefects. And the pathophyiological mechanisms remain controversial [15]. Spitznashas spectulated that abnormality of the retinal pigment epithelial postulates a reversal water transport from the choroid towards the neuroretina [14]. In addition, elevated levels of serum cholesterol may cause macular edema and hard exudation, key features of CSCR. For example, increased level of triglycerides is associated with macular edema and hard exudation. Traditional treatment includes blood circulation drugs and glucocorticoid antagonist. However, these drugs have the potential effects to cause interlayer effusion, recurrence, and/or visual distortion for retinal macular edema patients, which is a serious issue for visual acuity. Laser photocoagulation and PDT treatment seals RPE leakage by laser thermal effects, but the abnormal choroidal blood flow is not improved. They also have the potential side effects to induce non-selective coagulation necrosis on the adjacent tissue, such as the formation of central scotoma, the reduction of contrast sensitivity, and secondary CNV. Effects of anti-VEGF treatment for CSCR are not well studied. Therefore, large-scale multicenter clinically controlled trials are necessary to evaluate the efficacy and safety of anti-VEGF therapy for CSCR. Furthermore, virectomy is ineffective for CSCR. Thus, understanding the mechanism of angiogenesis, and discovering new drugs and therapeutic targets for CSCR are currently the major focuses.

Fenofibrate can activate PPARα, reduce ApoC-III mRNA expression in the liver, decrease the plasma ApoC-III, stimulate the expression of ApoAI genes, improve the lipoprotein lipase activity in adipose tissue, and accelerate the catabolism of TG-rich lipoprotein. Fenofibrate also improves the progression of diabetic retinopathy (DR) and promotes the absorption of macular edema through non-lipid-mediated 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 fenofi-

brate on cardiovascular risk and diabetes complications in type 2 diabetes [15, 16]. Taking 200 mg of fenofibrate daily did not improve visual acuity measures, but could significantly decrease the need for laser treatment in patients with DME and proliferative retinopathy, and it could promote 30% of the regression of the macular edema [17]. These findings have resulted in recommendations that fenofibrate be used as an adjunct treatment for type 2 diabetic with nonproliferative diabetic retinopathy [18, 19].

Propranolol, as a selective beta adrenergic receptor blocker, can block the membrane calcium channel, and effectively inhibit vascular spasm caused by vascular smooth muscle cell calcium overload. It can also reduce platelet adhesion and aggregation, stablize cell membrane, antagnoize sympathetic excitement, and block pathophysiological reactions caused by sympathetic nerve excitement. RAAS system is consist of renin-angiotensin-aldosterone system, of which angiotensin Ang2 can increase the viscosity of monocytes, and promote the formation of endothelial single layer [20]. At the same time, it promotes interations between vascular endothelial cells and leukocytes, and increases local secretion of cytokines, such as tissue necrosis factor. However, it can also promote cell apoptosis, and induce endothelial dysfunction, thrombosis, retinal tissue ischemia hypoxia, angiogenesis, and hyperplastic lesions [21]. Ang2 can accelerate the secretion of VEGF, and VEGF is endothelial specific growth factor [22], which plays an important role in diabetic retinopathy [23]. Researches have also confirmed that Ang2 improves the permeability of blood vessels, increases vascular endothelial oxygen pressure, induces sympathetic nervous system tension, and is assiosiated with retinal vascular tension and retinal degeneration [24]. Propranolol can reduce sympathetic nervous excitement, decrease the secretion of a variety of angiogenic factors especially VEGF [25], block the production of renin from renal cells, and therefore reduce the Ang2 level in the body. Together, these suggest that propranolol might have huge potential value of treating retinopathy.

We previously reported that fenofibrate acts as an efficient medicine for the treatment of CSCR. This study further showed that proper useage the capability of fenofibrate to delay the development process of acute CSCR. After 8 weeks, the CST, SFV, SFVD and SFHD were decreased in group B ($P<0.05$), and further reduced in group A ($P<0.05$). Fenofibrate alone improves blood hypercoagulable state. Taking propranolol (60 mg) and fenofibrate (200 mg) could improve the visual acuity measures, and significantly decrease the need for using laser treatment in patients with DME and proliferative retinopathy [19]. Therefore, combination of fenofibrate with propranolol is an efffective medication regimen in treating acute CSCR.

Conclusion

Our results showed the effectiveness of fenofibrate with propranolol as a treatment option for acute CSCR. Following therapy, there was a significant reduction in the CST, SFV, SFVD, and SFHD indices, and visual acuity was improved in eyes with acute CSCR. This study also has some limitations, including the small number of patients, single type of acute CSCR and relatively short follow-up period. Propranolol may counter the effect of catecholamines in the pathology and clinical conditions of CSCR; however, more evidence is needed before they can be recommended.

Acknowledgements

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Disclosure of conflict of interest

None.

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