Int J Clin Exp Med 2016;9(8):15996-16005
www.ijcem.com /ISSN:1940-5901/IJCEM0028527

Original Article

Effect of fenofibrate and aspirin on acute central serous chorioretinopathy

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Received March 17, 2016; Accepted June 12, 2016; Epub August 15, 2016; Published August 30, 2016

Abstract: Background: Central serous chorioretinopathy (CSCR) may result in serous elevation of the retinal pigment epithelium (RPE) and/or detachment of the neural retina due to RPE barrier dysfunction. Fenofibrate acts as an efficacy medicine could improve the vision and symptoms of patients in patients with CSCR. In this study, we continue to define the effectiveness of this new treatment strategy by comparing the results obtained in patients treated with fenofibrate and aspirin with those in a historic control group consisting of patients with CSCR who were only taking fenofibrate. Methods: Totally 60 patients (60 eyes) with a history of acute CSCR on fenofibrate were randomized into two groups: A combination of fenofibrate (200 mg) and aspirin (100 mg) was used in group A, whereas in group B, only fenofibrate (200 mg) was administered. They were taken before meals half an hour and 1 times per day for 8 weeks. The change of the best corrected visual acuity (BCVA) and coherence tomography [including mean central subfield thickness (CST), mean subretinal fluid volumn (SFV), mean subretinal fluid vertical diameter (SFVD), mean subretinal fluid horizontal diameter (SFHD)] were observed at 1, 2, 4, 8 weeks before and after treatment. Results: After treatment, the average baseline BCVA (logMAR) was 0.34 and the average BCVA (logMAR) was 0.23 in Group A. In group B, the average baseline BCVA (logMAR) was 0.35 and the average BCVA (logMAR) was 0.28 at study completion. The differences of improved BCVA before and after treatment between the two groups were statistically significant ($P<0.05$). Besides, the CST, SFV, SFVD and SFHD significantly decreased 49.5%, 78.8%, 79.3%, 90.5% and had statistically significant at the fourth follow-up compared with baseline (= 0.031, = 0.014, = 0.022, and = 0.019, respectively) in group A. The CST, SFV, SFVD and SFHD significantly decreased 37.0%, 57.2%, 58.8%, 73.0% and had statistically significant at the fourth follow-up compared with baseline (= 0.046, = 0.036, = 0.049, and = 0.057, respectively). There were significant difference for the CST, SFV, SFVD and SFHD at the fourth follow-up in both groups (all $P<0.05$). Conclusion: Fenofibrate has more clinical efficacy in the treatment of patients with CSCR combined with asprin than fenofibrate only.

Keywords: Fenofibrate, asprin, CSCR, vision, OCT

Introduction

Central serous chorioretinopathy (CSCR) may result in serous elevation of the retinal pigment epithelium (RPE) and/or detachment of the serous retina [1]. Von Gräfe (1866) first reported this pathology with common clinical symptoms, such as visual distortion, floating shadows, and vision loss. The incidence of this disorder continues to increase. CSCR is reported to be associated with uncontrolled hypertension and preeclampsia, and has been described in patients undergoing hemodialysis or systemic steroid use [2-4]. It is classically described as affecting middle-aged people, with a male prevalence, and in personality types who exhibit a high stress response [5, 6]. It possesses a long course, severe symptoms, and has been a key topic in recent research. Diamox, thermal laser or photodynamic therapy are the main therapeutic approaches at present. Unfortunately, many cases of acute CSCR are not eligible for or do not respond to treatment with thermal laser or photodynamic therapy.

Fenofibrate could interfere with the multiple mechanisms of CSCR, by reducing plasma lipids, improving endothelial function, inhibiting excessive expression of inflammatory factors, reducing apoptosis in the retina, and inhibiting the formation of vascular endothelial growth factor (VEGF). Aspirin possesses antiaggregant effects and it is effective in reducing serum levels of PAI-1, which is elevated in patients with CSCR [7]. We previously reported that fenofibrate acts as an efficacious medicine in patients with CSCR [8].

To define the effectiveness of this new treatment strategy, we performed a study comparing the results obtained in patients treated with fenofibrate and aspirin with those in a historic control group consisting of patients with CSCR who were only taking fenofibrate.

Subjects and methods

Patients and study design

A prospective randomized control study was conducted. In order to minimize imbalance from important non-experimental factors such as age, patients were randomly allocated to groups. 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 and the First People's Hospital of Shunde. The patients, who were 36 to 60 years old (average age 52.2±8.9 years), were randomly divided into two groups. A combination of fenofibrate (200 mg) and aspirin (100 mg) was used in group A, whereas in group B, only fenofibrate (200 mg) was administered. Both groups were treated once per day for 8 weeks. Patients did not have other ocular histories, systemic diseases, or histories of taking anti-hypertensive or anti-depressant medication. Furthermore, none of the patients were pregnant or lactating. Visual acuity and optical coherence tomography [9] [including mean central subfield thickness (CST), mean subretinal fluid volume (SFV), mean subretinal fluid vertical diameter (SFVD), mean subretinal fluid horizontal diameter (SFHD)] were measured before treatment and at 2, 4, 6, and 8 weeks after treatment. The sample size was set at 30 based on the equation n = 15.6R+1.6 under 80% confidence.

Follow-up time was divided into several periods and plotted using a mixed model analysis. Since time on drugs ranged from 1 day to 14 days, 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), 0-2 weeks, 2-4 weeks, 4-6 weeks, and 6-8 weeks.

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 routine eye examination, optical coherence tomography (OCT) examination and fundus fluorescein angiography (FFA) examination [10]. In accordance with CSCR diagnostic criteria, clinical presentation of the disease included: (1) clinical manifestations of visual impairment, central scotoma (blind spot), visual darkening, discoloration, deformation, etc.; (2) OCT examination showing macular edema or discoid antihalo; (3) FFA examination showing a diffuse wide spreading of fluorescein (90%) or smoke-like leakage (10%) that fills a localized space under the retina.

Exclusion criteria

Key exclusion criteria included subjects who had a history of retinal vascular diseases including diabetic retinopathy, previous retinal vein occlusion affecting the retina, diabetic macular edema, exudative age-related macular degeneration (AMD), or a history of uveitis within the study eye. Other exclusion criteria were: (1) a history of allergies, trauma, or surgery on the eye or kidney; (2) previous diagnosis of other ocular diseases, such as keratopathy; (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)

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 (22-52)	0.356	0.695
Sex (Male to female)	26/4	27/3	0.752	0.852
Laterality (right:left)	18/12	16/14	0.534	0.773
Spherical equivalent refractive error (diopters)				
Mean ± SD (Range)	-1.62±2.20 (-3.5-2.75)	-1.84±2.15 (-3.75-3.25)	0.032	0.342
Duration of CSCR (days)	10.56±4.15 (1-10)	10.19±5.54 (1-9)	0.683	0.615
Number of eyes with PED (%)	4 (13.3%)	3 (10.0%)	0.935	0.705
Fbg (mmol/L)	5.33±1.78	5.48±1.59	0.824	0.932
SC (mmol/L)	64.14±11.68	63.19±13.87	0.717	0.661
BMI	23.19±4.66	23.62±3.97	0.885	0.397
Smoking stutus no./total no.(%)				
Nerver Smoked	12 (40)	10 (33.3)	0.011	0.628
Former Smoker	6 (20)	9 (30)	0.021	0.553
Current Smoker	12 (40)	11 (36.7)	0.013	0.743

Abbreviations: PED, Pigment epithelium detachment; SD, Standard deviation; BCVA, Best corrected visual acuity.

any subject unwilling to give informed consent; (6) previous treated CSCR.

Observation criteria

All cases were confirmed by systemic eye tests, fundus imaging, FFA examination, and OCT examination and compared in patients before treatment and up to 8 weeks after treatment. Safety indicators included blood pressure, blood lipids, routine laboratory tests on urine and feces, hear 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 [11].

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 retinal detachment, and/or other circumstances that required vitrectomy combined with intraocular laser surgery.

Statistical analyses

All values were 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).

Results

Baseline characteristics

The average patient age was 41, ranging from 22 to 52 y 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 detail are presented in **Table 1**.

The best corrected visual acuity

In group A (combination of fenofibrate (200 mg) and aspirin (100 mg)), the average baseline

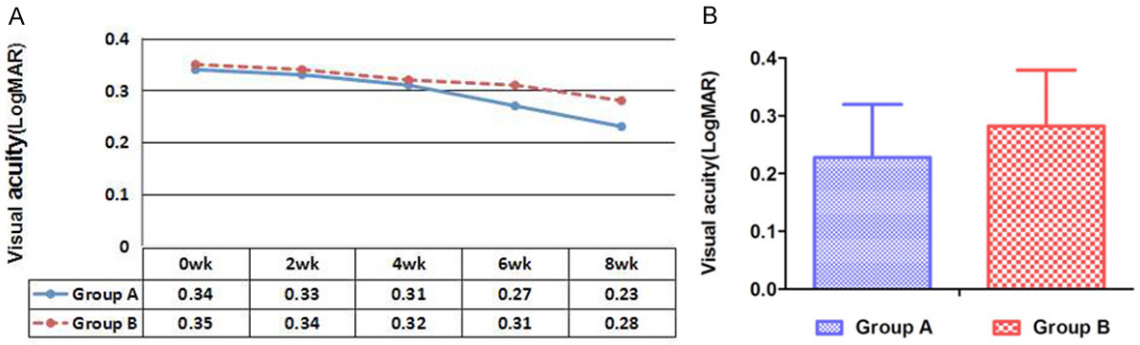

Figure 1. Time course of the mean BCVA of eyes with acute central serious chorioretinopathy that underwent drugs treatment in both groups. A. The Time course of the mean BCVA in each group at 2, 4, 6, and 8 weeks after treatment.The BCVA is significantly better at 8 weeks than at baseline in both groups. 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.

BCVA (logMAR) was 0.34 (range: 0.16-0.48) and the average BCVA (logMAR) was 0.23 (range 0.10-0.46) at study completion. LogMAR had statistically significantly decreased at the fourth follow-up period compared with baseline (P = 0.02). In group B (fenofibrate (200 mg) alone), the average baseline BCVA (logMAR) was 0.35 (range: 0.14-0.49) and the average BCVA (logMAR) was 0.28 (range 0.12-0.46) at study completion. LogMAR had statistically significantly decreased at the fourth follow-up period 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**).

OCT result analysis

The average baseline CST (μm) was 341.56 (range: 308.28 to 389.17) and the baseline SFV (μl) was 1.03, ranging from 0.48 to 1.89 in group A , whereas, in group B, the average baseline CST (μm) was 344.91 (range: 310.84 to 382.67) and the baseline SFV (μm) was 1.06, ranging from 0.51 to 1.78. In addition, the average baseline SFVD (μm) and baseline SFHD (μm) were detected, in group A the value were 136.28 (range: 109.33 to 166.72) and 2394.69 (range: 1931.41 to 2662.95), in group B the value were 136.89 (range: 116.55 to 163.46) and 2284.17 (range: 1908.91 to 2648.98). At study completion, we observed and compared these index again between these two groups: In group A, average CST was 175.24 μm (range: 106.51-226.89 μm) (**Figure 2A**) and the baseline SFV was 0.22, ranging from 0.06 to 0.44 (**Figure 2B**). The Average SFVD was 27.42 μm (range: 11.26-67.89 μm) (**Figure 2C**) and the SFHD was 227.93, ranging from 105.41 to 369.56 (**Figure 2D**). In group B, Average CST was 218.64 μm (range: 132.41-238.96 μm) and the baseline SFV was 0.48, ranging from 0.11 to 0.78. The Average SFVD was 55.63 μm (range: 37.53-106.56 μm) and the SFHD was 622.16, ranging from 511.07 to 769.83. We found the CST, SFV, SFVD and SFHD significantly decreased 49.5%, 78.8%, 79.3%, 90.5% and had statistically significant at the fourth follow-up compared with baseline (= 0.031, = 0.014, = 0.022, and = 0.019, respectively) in group A, and in group B these four index had the same change trend as following: The CST, SFV, SFVD and SFHD significantly decreased 37.0%, 57.2%, 58.8%, 73.0% and had statistically significant at the fourth follow-up compared with baseline (= 0.046, = 0.036, = 0.049, and = 0.057, respectively). Finally, we ascertain twenty-four eyes (80%) in group A, and eighty eyes (60%) in group B within the study demonstrated complete resolution of SFV at treatment completion, which ranged from 1 week to 8 week as time of resolution. There were significant difference for the CST, SFV, SFVD and SFHD at the fourth follow-up in both groups (all P<0.05).

Typical cases

We also present two representative cases with different outcomes after the two different treat-

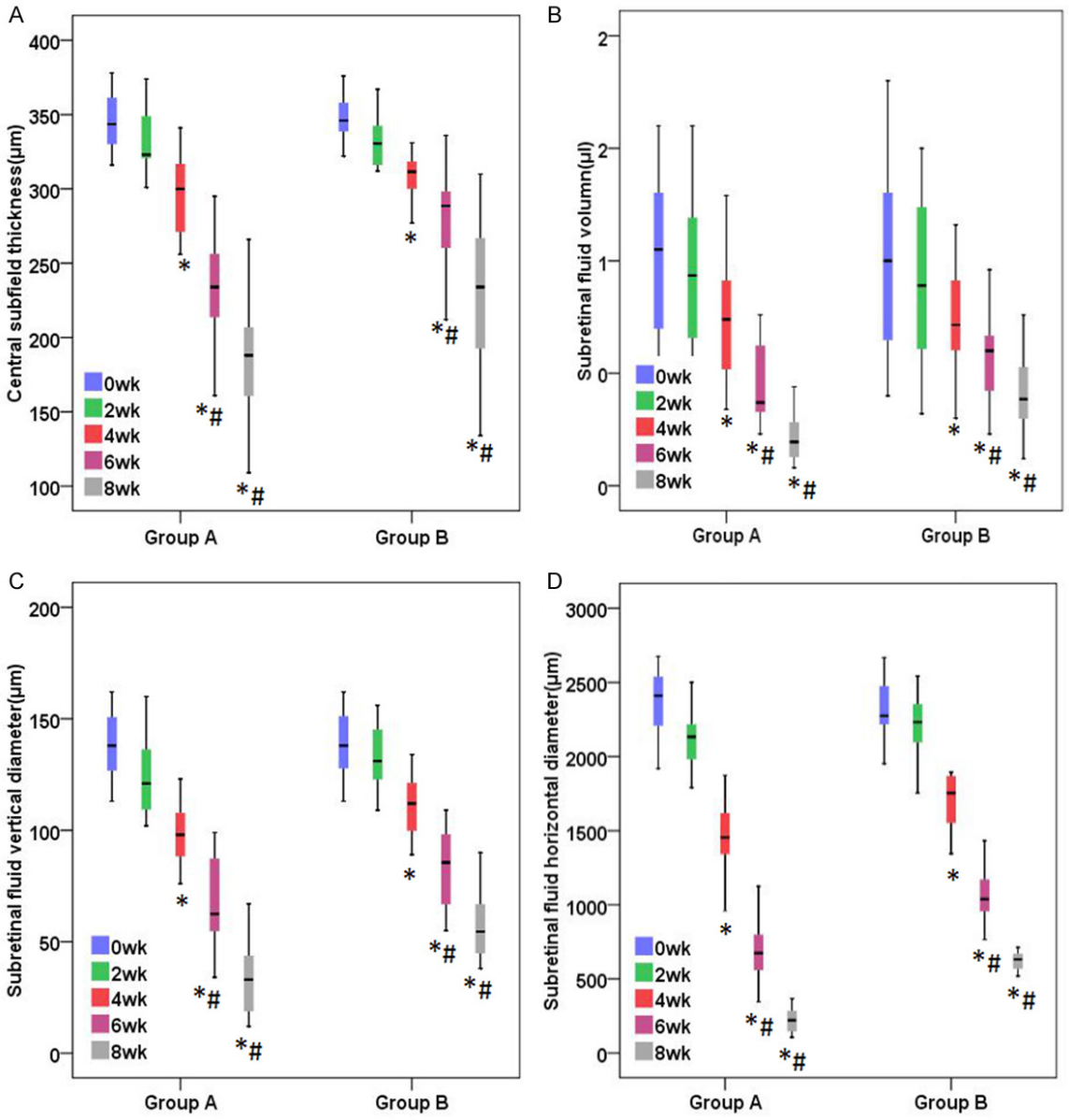

Figure 2. Alterations in macular area by optical coherence tomography. The trend of subretinal fluid reduction measured by OCT at baseline and follow up visits at 2, 4, 6 and 8 weeks after the onset of treatment. Mean Central subfield thickness (μm) (A), Mean Subretinal fluid volumn (μl) (B), Mean Subretinal fluid vertical diameter (μm) (C), Mean Subretinal fluid horizontal diameter (μm) (D) were declined at 8 weeks. The sample size was 30 cases for group A and 30 cases for group B throughout the study. The top and bottom of each box represent the 25th and 75th percentiles of the data and the lines in the box show the medians. The bars extending above and below each box represented 1.5 times the interquartile range (difference between the 25th and 75th percentiles), and the open circles were outlier values. Before therapy *vs* after therapy, *P<0.05; Group A *vs* Group B, #P<0.05.

ments, although several pretherapy findings were similar (**Figure 3A**, **3C**). In both cases, the fundus appearance, fluorescein angiography, indocyanine green angiography and OCT findings, but not fixation properties, were similar at baseline. However, the response to different treatments was different (**Figure 3B**, **3D**).

The clinical safety and validity

Compared with before therapy, the item (including GPT, GOT, UCr, BUN) had no obvious change at 8 weeks after therapy in both groups (all P>0.05, **Table 2**). Totally 8 weeks after treatment, the difference between two drugs for

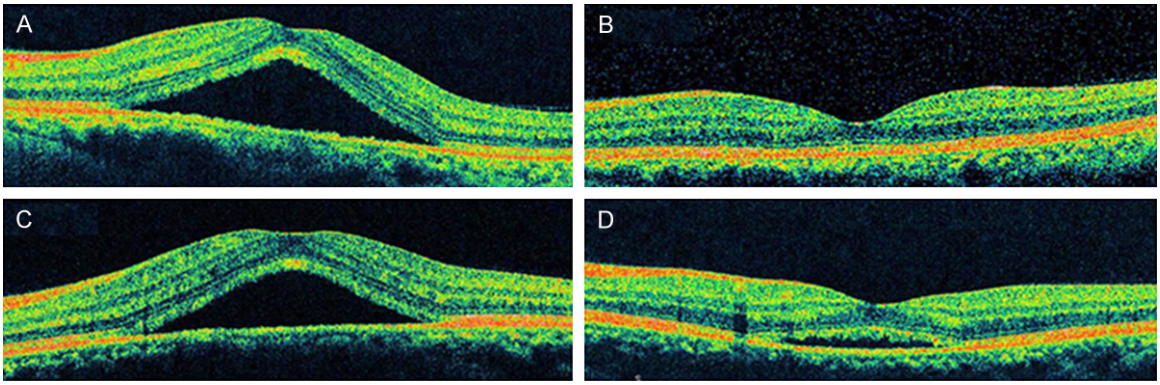

Figure 3. OCT images generated using the Cirrus HD-OCT 4000 (Zeiss, Germany) in (A, B) a 42-year-old female with CSCR in group A and (C, D) a 50-year-old female with acute CSCR in group B. In the group A, the OCT images of pre-therapy revealing the retinal detachment of macular area (A), and the OCT images at post-therapy 8 week show the decreasing retinal detachment in the macular area (B); In the group B, the OCT images of group B pre-therapy showing the retinal detachment in the macular area (C), and the OCT images at post-therapy 8 week show the integrity retinal layer of macular area (D).

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})	22.56±7.14	23.81±6.71	24.02±7.53	23.99±6.99	0.096	0.641
GOT (μmol·L^{-1})	29.12±6.59	27.32±5.29	28.91±6.12	29.82±6.85	0.353	0.887
SDP (mmHg)	131.19±16.21	119.74±17.75*	129.87±18.61	127.61±20.74$^{\#}$	8.541	0.032
DBP (mmHg)	84.54±9.64	74.21±6.93*	85.37±9.15	83.96±10.17$^{\#}$	10.543	0.015
TG (mmol·L^{-1})	1.08±0.29	0.75±0.19*	1.14±0.19	0.81±0.22*	0.276	0.966
TC (mmol·L^{-1})	4.61±1.02	3.19±1.35*	4.83±1.16	3.32±0.98*	0.642	0.414
UCr (μmol·L^{-1})	60.64±18.09	56.22±14.57	62.34±19.66	61.71±16.82	0.967	0.326
BUN (μmol·L^{-1})	3.54±0.89	3.42±0.67	3.78±0.92	3.61±0.56	0.561	0.615

Note: Before therapy *vs* after therapy, *P<0.05; Group A *vs* Group B, $^{\#}$P<0.05.

SBP and DBP was statistically significant, whereas the difference of blood lipid (including TC and TG) was not statistically significant (all P>0.05), as shown in **Table 2**.

Discussion

CSCR is a self-limiting disease and the central vision of about 70% of patients can be recovered in 3 to 6 months. Without early treatment, long-term macular edema will damage visual function in some patients, which ultimately leads to degeneration of visual cells. The exact cause of CSCR is not yet fully understood, but various studies have shown that it might be associated with corticosteroids, alcohol intake, or decreased function of the immune system. Although the pathogenesis of CSCR was not clear, some studies have reported that damage to the RPE could cause damage to the zonula occludens and breakdown of the RPE barrier. However, other studies have reported that choroidal circulation disorder causes damage to the RPE. 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.

Drugs which improve blood circulation and glucocorticoid antagonists have been the traditional treatments for this disease. However, these types of drug have 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 and photodynamic therapy (PDT) treatment only stop the RPE leakage using laser thermal

effects, but they do not reduce the abnormal choroidal blood flow. They also have the potential to elicit non-selective coagulation necrosis on tissue adjacent to the lesion area, which would result in several adverse effects, such as the formation of central scotoma, the reduction in contrast sensitivity, and secondary choroidal neovascularization (CNV). There are only a few studies on anti-VEGF treatment for CSCR, therefore, large-scale multicenter clinically controlled trials are necessary to evaluate the efficacy and safety of anti-VEGF therapy for CSCR. In addition, vitrectomy 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 current ophthalmic research.

Fenofibrate is the third-generation phenoxy aromatic acid derivative tune pharmaceuticals. It is a PPARα agonist which has several functions, such as activating PPARα, reducing ApoC-III mRNA expression in the liver, decreasing plasma ApoC-III, stimulating the expression of ApoAI genes, improving lipoprotein lipase activity in adipose tissue, and accelerating the catabolism of triglyceride (TG)-rich lipoprotein. Fenofibrate can also lower plasma TG in patients with hyperlipidemia, and it also has non-lipid mediation mechanisms that can enhance endothelial function, anti-inflammation, and anti-oxidative stress effects.

Walke *et al* [12] observed two cases of healthy elderly subjects with normal lipid levels who took fenofibrate orally for 7 days, and it was found that fenofibrate reduced oxidative stress, induced eNOS generation, and showed a protective effect on vascular endothelial function. By culturing neurosensory cells with high levels of glucose for 18 days, Trudeau *et al* [13] found that fibronectin expression increased, while fibronectin and collagen IV expression decreased after fenofibrate treatment. These outcomes delayed aging of the basilar membrane of the RPE layer and reduced the production of end-products of advanced glycation. Therefore, fenofibrate treatment prevents excessive thickening of the basilar membrane, and reduces leakage from the outer retinal vascular permeability barrier. Moreover, Chen *et al* [14] found that fenofibrate has a direct role in retinal tissue through PPARα; it significantly reduces the expression of various inflammatory cytokines, such as MCP-1, and also decreases the expression of VEGF and the activity of HIF-1α. Fenofibrate also delays the progression of diabetic retinopathy (DR) and promotes the absorption of macular edema through non-lipid mediation effects.

Keech *et al* [15] found that fenofibrate could delay the existing development process of DR. Taking 200 mg of fenofibrate daily could significantly decrease the need to use laser treatment in patients with diabetic macular edema and proliferative retinopathy, and its use accounted for 30% absorption of macular edema. This may be related to the specificity of the target PPARa; PPAR is widespread amongst endothelial cells and is associated with inflammation, nerve injury, and oxidative damage [16, 17]. Fenofibrate could activate the production of PPAR, the inhibition of VEGF receptor 2, and the neovascularization in umbilical endothelia. There is little research about whether the same PPAR is present in retinal endothelial cells, and PPAR agonists in DR show anti-inflammatory effects, antioxidant effects, and inhibition of angiogenesis through the same mechanism.

The FIELD study [18] enrolled 9795 cases of type 2 diabetes patients (50-75 years old). The impact of delaying DR progression by lowering blood glucose, blood pressure, and blood lipids was evaluated. It was found that maintaining low plasma lipids did not reduce the number of laser treatments needed, whereas taking fenofibrate orally reduced the frequency of laser treatments for patients with DR, slowed the progression of DR, and promoted the absorption of macular edema. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [19] showed similar results, which provides new evidence for the relevance of applying fenofibrate for the prevention and treatment of DR. Fenofibrate not only enhances the activity of superoxide dismutase, but it also improves vascular endothelium-dependent delayed reaction, prevents the occurrence of DR, and contributes to avoiding laser treatment by inhibiting apoptosis of retinal endothelial cells, preventing cell migration, and reducing the local cellular inflammatory response.

Aspirin is a non-steroidal anti-inflammatory drug. Its main role is as an antipyretic, analge-

sic, anti-inflammatory and antirheumatic, and it inhibits platelet aggregation. Aspirin acts primarily through irreversible inhibition of cyclooxygenase-1 (cox1) and cyclooxygenase-2 (cox2), which prompts the decline in prostaglandin (PG) expression [20]. The DAMAD research team have administered aspirin to patients with diabetic retinopathy for more than 3 years, and have found that it can alleviate the majority of cases of retinopathy [21]. In a diabetic rat model, Lorenzim *et al* [22] observed that a low concentration of aspirin can delay the progression of diabetic retinopathy. Later studies also showed that aspirin can prevent diabetic retinopathy [23, 24]. Nowak *et al* [25] found that aspirin helps in the early treatment of AMD, whereas other studies have shown that long-term use of aspirin can lead to AMD, or that there was no clear correlation between the two [26, 27]. Whether aspirin can be used in AMD requires more evidence-based trials for verification.

We previously reported that fenofibrate acts as an efficacious treatment in patients with CSCR. This study has found that, with appropriate use of fenofibrate, the development of acute CSCR can be delayed. After 8 weeks of treatment, CST, SFV, SFVD, and SFHD values were statistically significantly lower ($P<0.05$) in group B (fenofibrate alone), but the decrease was greater ($P<0.05$) in group A (fenofibrate and aspirin) after treatment. Fenofibrate alone is by no means able to prevent vascular endothelial injury and significantly improves the blood hypercoagulable state. When administered orally, aspirin is rapidly absorbed, and excretion in urine is almost entirely in the form of metabolites, without obvious side effects. Fenofibrate has cholesterol, inhibiting new blood vessels, and improving vascular endothelial function, whereas aspirin inhibits platelet aggregation and angiogenesis, controlling the expression of inflammatory cytokines, and reducing leukocyte adhesion function [28]. Therefore, we combined fenofibrate with aspirin to treat acute CSCR. This study shows that, when combined (group A), fenofibrate and aspirin significantly reduce CST and SFV, and improve BCVA when compared with fenofibrate alone (group B). After combination therapy, CST, SFV, SFVD, and SFHD values in group A were significantly lower ($P<0.05$) compared with before treatment. In this study, none of the patients manifested adverse reactions to the two drugs. Therefore, administration of aspirin and fenofibrate enabled a more rapid recovery of BCVA and absorption of macular edema in comparison with the fenofibrate alone group.

Conclusion

The results of this study seem to demonstrate the effectiveness of a combination of lower-dose aspirin and fenofibrate in the treatment of acute CSCR. In our series, gastrointestinal risks did not occur, probably because of the young age of our patients, and their lack of history of ulcerative gastric disease. Our study has limitations, including its retrospective nature and small sample size. Further studies will be needed to be able to individualize the oral dosage and duration of administration of the drugs and to clarify the change of individual factors in the onset of this multifactorial illness.

Acknowledgements

This work was supported by National Natural Science Foundation of China (No: 81160118, 81660158 and 81400372); Jiangxi Province Voyage Project (No: 2014022); Natural Science Key Project of Jiangxi Province (No: 20161ACB21017); Science and Technology Platform Construction Project of Jiangxi Province (No: 2013116); Youth Science Foundation of Jiangxi Province (No: 20151BAB215016); Technology and Science Foundation of Jiangxi Province (No: 20151BBG70223); Education Department Scientific Research Foundation (No: GJJ14170); Health Development Planning Commission Science Foundation of Jiangxi Province (No: 20155154); The Scholar of Ganjiang River (2015). We thank Fei Dong (Department of Ophthalmology, University of Cincinnati, United States) and Yi Zhou (Stowers Institute for Medical Research, Kansas City, United States) for reviewing the paper.

Disclosure of conflict of interest

None.

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