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K. MORAWSKI[1], A. KLONOWSKA[1], A. KUBICKA-TRZASKA[1,2], J. WORON[3], B. ROMANOWSKA-DIXON[1,2]

CENTRAL SEROUS CHORIORETINOPATHY INDUCED BY DRUGS METABOLIZED BY CYTOCHROME P450 3A4

[1]Clinic of Ophthalmology and Ocular Oncology, University Hospital, Jagiellonian University Medical College, Cracow, Poland;
[2]Chair of Ophthalmology, Faculty of Medicine, Jagiellonian University Medical College, Cracow, Poland;
[3]Chair of Clinical Pharmacology, Faculty of Medicine, Jagiellonian University Medical College, Cracow, Poland

The purpose of this study was investigate whether replacing or discontinuing drugs that are inhibitors or substrates of cytochrome P450 3A4 (CYP3A4) may improve the clinical course of central serous chorioretinopathy (CSC). A retrospective observational study included 43 patients with active CSC. Twenty seven patients (32 eyes, group 1) were using drugs that act as substrates or inhibitors of CYP3A4. In 25 of these 27 patients, treatments including steroids, calcium channel blockers, anticoagulants, statins, beta-adrenolytics, angiotensin receptor antagonists, antidepressants, muscarinic receptor antagonists, phosphodiesterase type 5 inhibitors, and others were discontinued or replaced with medications not affecting CYP3A4. Sixteen patients (19 eyes, group 2) not using any medication that affects CYP3A4, were given eplerenone, rifampicin, or laser treatment. Main outcomes measures were assessed by functional and anatomical images obtained using multimodal imaging techniques. The average follow-up time was 12 months. In group I after discontinuing or replacing substrates or inhibitors of CYP3A4, improvements were observed in 18 patients (22 eyes). None of the patients that were using drugs affecting CYP3A4 improved with eplerenone therapy, however, all 18 patients improved after discontinuing the drugs. All these drugs had a blocking effect on eplerenone therapy. Best corrected visual acuity (BCVA) improved in 14 eyes, remained unchanged in 5 eyes, and worsened in 3 eyes. In 21 of the 22 eyes, subretinal fluid absorption was observed with optical coherence tomography (OCT). Mean central retinal thickness decreased from 361 μm to 219 μm. One patient (2 eyes) was unable to change treatment (due to neoplasm), one patient (1 eye) did not agree to change or stop treatment, and seven patients (7 eyes) were lost to follow-up. Of the 16 patients (19 eyes) who were treated with eplerenone, rifampicin, or laser, improvements were observed in 14 patients (16 eyes), two patients (2 eyes) were lost to follow-up, and CSC worsened in 1 eye. We concluded that patients with CSC should not take substrates or inhibitors of CYP3A4. These drugs should be replaced with alternatives that act through other metabolic pathways.

Key words: *central serous chorioretinopathy, best corrected visual acuity, cytochrome P450 3A4, inhibitors and substrates of CYP3A4, blood-retinal barrier, mineralocorticosteroid receptors*

INTRODUCTION

Clinical symptoms of central serous chorioretinopathy (CSC) include reduced vision associated with metamorphopsia and micropsia, often accompanied by localized round serous retinal detachment in the macula (1). The pathophysiology of CSC remains unclear. Based on swept-source optical coherence tomography (OCT) observations, CSC belongs to the recently described group of pachychoroid spectrum diseases (2). While evidence for a genetic contribution to the disease exists, the current understanding of the pathogenesis of CSC emphasizes the role of the choroid, where the disease has its origin (3).

CSC mainly affects the middle-aged population, and mostly men who exhibit type A behaviors (4). Mental stress, hypertension, sleep disturbances, alcohol abuse, systemic lupus, Cushing's disease, *Helicobacter pylori* infection, exogenous steroid use, and psychopharmacologic medication may trigger or intensify the course of CSC (5). Most of the above-mentioned risk factors share a common feature: elevated levels of endogenous glucocorticosteroids (GC) in the blood. In the retina, GC are capable of cross-binding with mineralocorticosteroid (MR) receptors, producing identical effects to MR-specific aldosterone binding (6, 7). Inappropriate activation of the MR receptor by GC causes dilatation of choriocapillaris and leakage of fluid under the neurosensory retina, leading to its serous detachment. Eplerenone inhibition of MR receptors prevents binding and activation by GC, thereby preventing this damaging cascade (8-10).

Inactivation of CYP3A4 by drugs has important clinical significance, as CYP3A4 metabolizes approximately 60% of therapeutic drugs, and inhibition frequently causes unfavorable drug-drug interactions and toxicity. Clinical outcomes in the case of CYP3A4 inactivation depend on numerous factors associated with the enzyme, drugs, and patient characteristics (11). On the other hand, drugs such as rifampicin, which is known to induce cytochrome P450 CYP3A4, therefore, could alter the metabolism of steroids and cause regression of CSC symptoms (12, 13).

We hypothesized that CYP3A4 inducers may improve the course of CSC, whereas inhibitors or substrates of CYP3A4 may lead to the development or *de novo* activation of the disease, or may exacerbate its clinical course. Discontinuing drugs that act as inhibitors or substrates of CYP3A4 should result in resolution of the disease.

The aim of this study was to analyze whether discontinuing or switching to another drug that is not a mechanism-based CYP3A4 inhibitor can benefit patients with CSC.

MATERIALS AND METHODS

We performed an retrospective study of patients who were referred to the Clinic of Ophthalmology and Ocular Oncology, University Hospital in Cracow, Poland with a diagnosis of acute and chronic CSC. The inclusion criteria for the study were: patients with active CSC with the presence of subretinal fluid confirmed by OCT. The exclusion criterion was: the presence of any other ophthalmic disease. In all cases, ophthalmic examination was performed including best corrected visual acuity (BCVA) assessment, slit-lamp examination, funduscopy, tonometry, fluorescein angiography (FA; TRC-50EX Retinal Camera, Topcon) and spectral domain OCT (SOCT; 3D-OCT 1000, Topcon; Copernicus HR, Optopol, Poland). Data on ophthalmic examinations, age, sex, duration of symptoms, number of relapses, associated systemic diseases, risk factors, medications used, cortisol and aldosterone serum levels, and previous treatment were collected. The variables studied (age, BCVA before and after treatment) were characterized by calculating their basic parameters (mean, standard deviation). The average follow-up time was 12 months, patient were examined every month. The patients were divided into two groups. Group 1 included twenty-seven patients (32 eyes) who used drugs that act as inhibitors or substrates of CYP3A4 and were asked to discontinue therapy, if possible, or to switch to another drug that is not a mechanism-based CYP3A4 inhibitor. In this group of patients in 25 cases medications that were discontinued or replaced. Before switching the medications, the current patient's therapy was analyzed by specialists of a clinical pharmacology, cardiology or a general practitioner to ensure that desired therapy was maintained without using drugs affecting CYP3A4. If eplerenone was previously taken, it was continued. Otherwise, eplerenone was added to the established treatment regimen.

Sixteen of 25 patients (19 eyes) from group 2 who were not using drugs that act on CYP3A4 were treated with 50 mg of eplerenone once per day for three months. In the absence of any effect, eplerenone was substituted with rifampicin (300 mg twice per day for 3 months) or micropulse laser treatment (160-µm spot size, 0.2 s, 5% duty cycle). Patients were evaluated monthly and clinical data was collected from each patient, including results of BCVA, basic clinical examination, and OCT.

The institution where the work was completed: Clinic of Ophthalmology and Ocular Oncology, University Hospital, Cracow, Poland. 38 Kopernika Street, 31-501, Cracow, Poland.

RESULTS

The study included 43 patients (51 eyes). The average age of patients was 44 years (29 – 5 years), including 12 women and 31 men. The mean duration of symptoms was 6.8 month. Twenty-eight patient had acute type of disease, 15 patient had chronic type of disease. *Table 1* shows that only 9 patients were completely healthy, the remaining patients had various general diseases that could be risk factors such as: hypertension, peptic ulcers, systemic allergy, autoimmune diseases: systemic lupus, thrombosis, asthma, atopic dermatitis, endocrine disorders, glomerulonephritis. There was no presence of choroidal neovascularization or other ophthalmic diseases, such patients were not included in the study. Among all 43 patients with active CSC, 27 (32 eyes) were using drugs that were substrates or inhibitors of CYP3A4 (group 1). We recommended discontinuation, if possible, or replacement with a drug that does not interfere with CYP3A4. In this group of patients in 25 cases medications that were discontinued or replaced included: calcium channel blockers, anticoagulants, statins, beta-adrenolytics, angiotensin receptor antagonists, antidepressants, muscarinic antagonists, phosphodiesterase type 5 inhibitors, 5-alpha reductase inhibitors, diuretics, thiazides, antibiotics, *e.g.*, macrolides-clarithromycin, erythromycin, androgen receptor antagonists, steroids, and non-conventional intravenous therapies, including a cocktail of vitamins. One patient (2 eyes) could not change the therapy with bicalutamide used for prostate neoplasm treatment, another patient (1 eye) did not agree to change his treatment for depression, and 7 patients (7 eyes) were lost during a follow-up. *Table 2* shows systemic medications that act on CYP3A4 used by analyzed group of patients. Reduction of subretinal fluid in OCT or BCVA improvement were observed in 18 patients (22 eyes) after discontinuing or replacing the medication. Since our center is a reference center, all 18 patients had previously undergone ineffective attempted treatment or had previously used eplerenone. This is very significant since none of the patients who were previously using drugs affecting CYP3A4 improved under eplerenone therapy. However, symptoms and signs of CSC were not observed in any of the 18 patients four weeks after discontinuing the drug. The fastest and most powerful effects were observed with the withdrawal of steroids and calcium channel blockers, in particular, amlodipine, which was being used by seven patients. Improvements were based on reduced disease activity, assessed by decreased or complete

Table 1. Patients' data.

	Age (years)	**Sex** Female Male	**CRT before** µm	**CRT after** µm	**BCVA Before** Decimal/LogMAR	**BCVA After** Decimal/LogMAR	**Acute CSC**	**Chronic CSC**
Group 1	47.9	7 F 20 M	361	219	0.59 0.3Log MAR	0.75 0.17LogMAR	12	15
Group 2	38.7	5 F 11 M	330	218	0.59 0.3LogMAR	0.71 0.23LogMAR	4	12

Table 2. Systemic medications that act on CYP3A4 used by analyzed group 1 of patients.

Number of patients	Used treatment	Discontinued	Swichted
1	amlodipine atrovastatin doxazosin mesilas	no no no	lercanidipine rosuvastatin torazosin
2	amlodipine	no	lisinopril
3	amlodipine atrovastatin	no	valsartan rosuvastatin
4	doxazosin mesilas	yes	–
5	losartan hydrochlorothiazyde atorvastatin omeprazole	no yes no	valsartan – rosuvastatin pantoprazole
6	fluoxetin	yes	–
7	glicopyrronium	no	umeclidinium
8	sildenafil anabolic steroids	yes yes	– –
9	indapamide	yes	–
10	amlodipine	no	perindopril
11	non-conventional intravenous therapies including a multiple cocktail of vitamins and microelements	yes	–
12	acenocumarol	no	dabigatran etexilate
13	lymecycline	yes	–
14	budesonide	yes	–
15	amlodipine	no	telmisartan
16	rivaroxaban	no	dabigatran etexilate
17	amlodipine indapamide atrovastatin	no no yes	nebivolol quinapril –
18	amlodipine	no	telmisartan

absorption of subretinal fluid, usually accompanied by improved BCVA. The average recovery time was four weeks (range from 1 to 6 weeks). In 14 eyes, BCVA improved, remained unchanged in 5 eyes, and worsened in 3 eyes. Baseline mean BCVA in this group of patients was 0.59 (0.3 LogMAR) and increased to 0.75 (0.17 LogMAR). Subretinal fluid absorption, evaluated by OCT, was found in 21 of the 22 eyes. Mean central retinal thickness (CRT) decreased from a baseline 361 μm to 219 μm at the end of the follow-up. Morning serum cortisol level range from 12.3 to 26.47 μg/dl (mean: 18.17 μg/dl). In the evening serum cortisol concentration decreased and ranged from 3.95 to 14.27 μg/dl (mean: 8.27 μg/dl). The average serum aldosterone level was 298.8 pmol/l (range: 100 – 515 pmol/l).

Group 2 included 16 patients (19 eyes) not using drugs that affect CYP3A4 activity. All patients received first-line treatment with eplerenone and 9 of them (11 eyes) showed reduction of CRT and resorption of subretinal fluid. With eplerenone, 5 patients (6 eyes) did not improve and 2 patients were (2 eyes) were lost to follow-up. Of the 5 remaining patients (6 eye) who did not improve after eplerenone treatment, 4 (5 eyes) were treated with rifampicin. Improvements were obtained in 4 eyes and deterioration in 1 eye. In one patient in which eplerenone treatment was ineffective, micropulse laser treatment was performed with subsequent improvement. Overall, regression of CSC was observed in 14 patients (16 eyes) who were treated with either eplerenone, rifampicin, or laser (reduced CRT, absorption of subretinal fluid, or improved BCVA), 1 eye worsened, and 2 patients (2 eyes) were lost to follow-up. In 10 eyes, BCVA improved, but remained unchanged in 6 eyes and worsened in 1 eye. At baseline mean BCVA in this group of patients was 0.59 (0.33 LogMAR), and increased to 0.71 (0.23 LogMAR). Subretinal fluid absorption, assessed by OCT, was found in 16 of 17 eyes. Mean CRT decreased from 330 to 218 μm. In the morning, average serum cortisol level was 21.23 μg/dl (range: 8.2 – 32.6 μg/dl), and dropped to 8.66 μg/dl in the evening (range: 4.5 – 15.63 μg/dl). Average serum aldosterone level was 139 pmol/l (range 58 – 272 pmol/l).

DISCUSSION

Some studies suggest that use of certain drugs might be a risk factor for CSC. Among the listed drugs are those included in popular body-building supplements, such as pseudoephedrine, amphetamine and ephedra (4, 6). Additionally, CSC has been reported after use of phosphodiesterase-5 inhibitors such as sildenafil, which is a weak inhibitor of CYP3A4 (14, 15). In our study, one patient who was taking sildenafil and protein supplements including those found in body-building supplements. After discontinuing medications, the patient (male) showed complete regression of the disease with BCVA improvement and resorption of subretinal fluid.

In our study, a common feature of drugs used among patients from group 1 was their negative effect on CYP3A4. On contrary to these medications rifampicin acts as an inducer of CYP3A4 improving clinical course of CSC. Shulmann *et al*. postulated that rifampicin alter the metabolism of multiple drugs among others steroids, thereby reducing their serum levels (12). It has been proved that CSC pathomechanism is strongly associated with elevated serum levels of GC (16-18). Drugs that are inhibitors or substrates work in the opposite way, *i.e*., increasing steroid levels in the blood. In the group of patients using drugs affecting CYP3A4, morning cortisol levels were 18.17 μg/dl on average, and evening levels were 8.27 μg/dl. In the non-drug taking group, morning cortisol levels were 21.23 μg/dl on average, and 8.66 μg/dl in the evening, which does not confirm this theory. However, it should be noted that too few cortisol tests (22 patients) were performed to allow for adequate statistical analysis.

Another issue is the role of ocular cytochrome P450 CYP3A4 in the eye compared to other human organs. Cytochrome P450 is a superfamily of enzymes that play a role in oxidative metabolism, drug-metabolism, and detoxification in mammals (19). Zhang showed a limited role of this cytochrome in the retinal pigment epithelium and blood-retinal barrier (BRB), and limited function in eliminating drugs compared to activity in the liver (20). This is a similar situation to the blood-brain barrier (BBB), whereby tight junctions between endothelial and retinal pigmented epithelial cells separate and protect retinal neuronal cells from substances circulating in the blood (21). However, Siu *et al*. emphasize the strategic role of the cytochrome P450 system located in the retina in neutralizing factors that may diffuse across the BRB. These factors include exposure to different types of toxins, oxidative stress, and phototoxicity caused by short-wavelength high-frequency blue light and ultraviolet light. Drugs affecting CYP3A4 can also include different types of toxins (22).

It is noteworthy that the none of the patients in our study that were using drugs affecting CYP3A4 improved with eplerenone therapy, however, in all 18 patients who did show improvements, CSC activity was not observed four weeks after discontinuing the drugs. All these drugs had a blocking effect on eplerenone. It is noteworthy that in our study the best response to drug withdrawal was noted with amlodipine and steroids. A rapid and sustained response was also observed with discontinuation of other drugs including anticoagulants, such as acenocumarol and rivaroxaban and verapamil. Patients who were using other drugs affecting CYP3A4 activity and discontinued them showed improvement, including patients using lymecycline for rosacea, fluoxetine, escitalopram, trazodone, and opipramol for depression, atorvastatin for hypercholesterolemia, lercanidipine, doxazosin, losartan, and hydrochlorothiazide for hypertension, and glycopyrronium bromide for chronic obstructive pulmonary disease. Some patients were using non-medical products such as body-building supplements, illegal anabolic steroids, and even, multi-component homeopathic or vitamin drips for "strengthening". Gong *et al*. studied serum aldosterone levels, which were found to be higher in the unresolved CSC group compared to the resolved CSC group (23). The authors observed that subfoveal choroidal thickness and CRT decreased significantly after two weeks treatment with 40 mg per day spironolactone. In our study, we did not assess the serum levels of aldosterone at baseline and then at the end of a follow-up, however we found that a higher aldosterone level (298.8 pmol/l) was detected in the group of patients treated with drugs affecting CYP3A4 activity as compared to the group not taking those drugs (139 pmol/l).

The use of eplerenone in our study also had ocular and systemic consequences. Gromotowicz-Poplawska *at al*. provided evidence that the antithrombotic effect of eplerenone is nitric oxide-dependent and associated with inhibiting the adhesion of platelets, as well as normalizing endothelial function (24). In turn clinical evidence from multimodal imaging, such as localized areas of choroidal nonperfusion and lobular choroidal ischemia suggests that choroidal dysfunction is an important underlying cause of RPE dysfunction and subretinal fluid leakage in CSC. Sztechman *at al*. discussed the role of mineralocorticoid receptors (MRs) in regulation and pathological remodelling of the cardiovascular system and the therapeutic potential of pharmacological targeting of MRs in cardiovascular disease (25). Furthermore inappropriate or over-activation of the mineralocorticoid receptor in ocular cells and other tissues (such as brain, vessels) could link CSC with the known co-morbidities observed in CSC patients, including hypertension, coronary disease and psychological stress. This observation need to be clarify in further investigations.

The results of our study suggest that to achieve the regression of ocular symptoms in CSC patients taking drugs metabolized by the P450 cytochrome pathway, it may be necessary to discontinue or switch to another medication that is not a mechanism-based CYP3A4 agent.

Conflict of interests: None declared.

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Author's address: Dr. Krzysztof Morawski, Clinic of Ophthalmology and Ocular Oncology, University Hospital, Jagiellonian University Medical College, 38 Kopernika Street, 31-501, Cracow, Poland.
E-mail: krzysztofmmorawski@wp.pl