Ketoconazole in the Treatment of Central Serous Chorioretinopathy

Mohammad Riazi Esfahani, MD1,2 • Hamid Reza Torabi, MD3
Zahra Aalami Harandi, MD2 • Mohammad Zarei, MD3

Abstract

Purpose: The aim of this study is to measure the endogenous cortisol levels in the patients with central serous chorioretinopathy (CSCR) and also, evaluate the short-term effect of oral ketoconazole in the treatment of both acute and chronic CSCR.

Methods: In this prospective interventional case series 12 patients with acute CSCR and 7 patients with chronic CSCR (including one patient with bilateral chronic disease) were treated with oral ketoconazole 200 mg two times per day. Measurement of best corrected visual acuity (BCVA), macular thickness [Using optical coherence tomography (OCT)], and 24-hour urinary cortisol levels were done before and after one month of treatment.

Results: Abnormal elevated levels of 24-hour urinary cortisol were identified in 50% of cases at presentation and it reduced after treatment (P=0.03). In acute CSCR patients, pretreatment mean logMAR BCVA was 0.3±0.2 and improved to 0.1±0.1 after treatment (P=0.005). Also central macular thickness was significantly reduced after treatment (P=0.001). Complete or partial improvement in central macular thickness and BCVA were happened in four from eight eyes with chronic CSCR.

Conclusion: Oral ketoconazole (400 mg/day) may be a noninvasive and safe therapeutic option for patients with acute CSCR and may alter the clinical course of some patients with chronic disease.

Keywords: Central Serous Chorioretinopathy, Ketoconazole, Corticosteroid, Optical Coherence Tomography

Introduction

Central serous chorioretinopathy (CSCR) is an idiopathic disorder of outer blood-retinal barrier that is characterized by accumulation of subretinal fluid resulting in circumscribed elevation of the retina in the posterior pole. Acute CSCR usually occurs in healthy young individuals between the ages of 20-50 years and causes an acute localized serous detachment of the retina with mild to moderate visual acuity (VA) loss. In most cases, acute CSCR is self-limited and resolves spontaneously in 4-6 months, however severe visual loss is reported in 5% of cases. Recurrence may happen in about one third to one half of all patients. Chronic CSCR is a rare form, characterized by a long-term presence of subretinal fluid for more than 6 months in association with widespread pigmentary changes and atrophy of retinal pigment epithelium. Chronic CSCR is often progressive with waxing and waning course and with more serious visual outcomes than acute type.

Multiple routes of corticosteroid administration including oral, inhaled, intranasal, intravenous, intramuscular and topical and also, cushing disease have been reported as a risk factor for CSCR. Due to documented association of hypercortisolism with CSCR, some investigators have suggested reduction of endogenous cortisol levels for treatment of CSCR. Corticosteroid antagonists such as RU486 (Mifepristone) and ketoconazole may be used for this purpose. Ketoconazole is an anti-fungal agent which can inhibit the endogenous biosynthesis of cortisol and also can act as a glucocorticoid receptor antagonist. In this study we measured the endogenous cortisol levels in the patients with CSCR and also, assessed the short-term effect of oral ketoconazole in the treatment of both acute and chronic CSCR.

Methods

Between May 2008 and October 2009, twelve patients with acute CSCR and six patients with chronic CSCR (Including one patient with bilateral chronic CSCR) enrolled to this nonrandomized prospective interventional case series. All patients were informed about other therapeutic modality and the off-label situation of this therapy and signed on informed consent discussing side effects of ketoconazole.

Acute CSCR was characterized by duration of symptoms less than 6 months. Patients with long standing symptoms (More than 6 months) associated with characteristic fluorescein angiographic pattern, was defined as chronic form. Exclusion criteria were any other associated ocular disease, pregnancy, acute or chronic liver diseases or abnormal baseline liver enzymes, and history of steroid intake in any form during past 6 months.

Each patient underwent ophthalmic examination including best corrected visual acuity (BCVA) measurement, slit-lamp examination and fundoscopy at baseline and one month after treatment. Also, measurement of central macular thickness using optical coherence tomography (OCT) was done. Zeiss Cirrus HD OCT was used for central macular thickness measurement in acute cases and Heidelberg Spectralis OCT was used in chronic CSCR cases. Fluorescein angiography was performed at baseline. Systemic tests included 24-hour urinary cortisol and liver function tests at baseline and one month later.

After baseline examination, oral ketoconazole 200 mg two times per day was started for one month. Anatomical improvement was considered as a primary outcome and secondary outcome was VA recovery.

Results

The mean age of total 19 patients (12 cases with acute and 7 patients with chronic CSCR) was 39.4±7 years. Nine patients were men and ten were women.

Abnormal elevated levels of 24-hour urinary cortisol were identified in 50% of cases at presentation (Mean 136.1±116 µg/24hr) and it was reduced to 80.4±55 µg/24hr after treatment (P<0.03).

Acute CSCR group

See table 1. The mean age was 38.4±4 years and the mean duration before treatment was 24±10 days.

Ten patients had complete resolution of subretinal fluid (Documented by OCT) and had improvement in VA after treatment
In one case (Patient 4) partial resolution of subretinal fluid and VA improvement happened after one month, but after 3 months follow-up, complete recovery with VA of 20/20 was achieved. In another case (Patient 9) treatment was not resulted in any improvement, and after 4 months laser photocoagulation was performed for him.

Overall, the mean logMAR BCVA before treatment was 0.3±0.2 and after 1 month of treatment it was improved to 0.1±0.1. The difference was statistically significant (P=0.005).

Central macular thickness which measured using OCT, before and after treatment was 449.6±113 and 287.5±135 respectively and the difference was statistically significant (P=0.001).

The mean 24-hour urinary cortisol levels reduced from 152.2±128 µg/24hr at baseline to 96.6±57 µg/24hr after treatment (P=0.12).

Table 1. Characteristics of patients with acute central serous chorioretinopathy

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Sex</th>
<th>Eye</th>
<th>Duration of CSCR (Days)</th>
<th>Pretreatment BCVA</th>
<th>Posttreatment BCVA</th>
<th>Pretreatment Macular Thickness (µm)</th>
<th>Posttreatment Macular Thickness (µm)</th>
<th>Pretreatment U-24hr cortisol (µg/24hr)</th>
<th>Posttreatment U-24hr cortisol (µg/24hr)</th>
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CSCR: Central serous chorioretinopathy
BCVA: Best corrected visual acuity
*: 24-hour urinary cortisol level was not tested because of occupational limitation of patient for urine collection.

Figure 1. Pretreatment (Left) and posttreatment (Right) optical coherence tomography scan of a patient with acute central serous chorioretinopathy (Patient 7)
Chronic CSCR group
See table 2. The mean age was 41.1±10 and the pretreatment disease duration was 15.7±7 months. None of the patients had received other treatments before. Average pretreatment logMAR BCVA was 0.42±0.4 and improved to 0.3±0.2 after treatment with ketoconazole, which was statistically insignificant (P=0.09).

The average central macular thickness was reduced after treatment, however, the difference between the mean central macular thickness before treatment and after treatment was not significant (P=0.09).

Anatomically, the lesions of 3 patients (Patients 2, 5 and 7) improved by 1 month and VA recovered (Figure 2). All of them had higher baseline VA (20/25) than others (From 20/200 to 20/40). Also, patient 3 had partial improvement. Other patients had minimal or no changes in VA or macular thickness.

Before treatment, 24-hour urinary cortisol levels were 119.8±97 µg/24hr and decreased to 53.6±36 µg/24hr after treatment (P=0.1).

<table>
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<th>Eye</th>
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<th>Pretreatment BCVA</th>
<th>Posttreatment BCVA</th>
<th>Pretreatment Macular Thickness (µm)</th>
<th>Posttreatment Macular Thickness (µm)</th>
<th>Pretreatment U-24hr cortisol (µgr/24hr)</th>
<th>Posttreatment U-24hr cortisol (µgr/24hr)</th>
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</tbody>
</table>

CSCR: Central serous chorioretinopathy
BCVA: Best corrected visual acuity

Figure 2. OCT scan of a patient with chronic central serous chorioretinopathy before (Left) and after treatment (Right)

Complications
No liver enzyme elevation or other side effects were observed in any of the cases and no cases stopped taking the medication.

Decrease in BCVA was found in any of the patients.
Discussion

In most cases, acute central serous retinopathy (CSCR) resolves spontaneously during 4-6 months\textsuperscript{2} and VA returns to \(0.20\) or better\textsuperscript{17,18}, however, some of the patients fail to recover and experience recurrent attacks and approximately 5% of all CSCR cases may develop severe visual loss\textsuperscript{3,4}.

For shortening the symptomatic period and lowering the rate of RPE degeneration, some ophthalmologists consider early treatment\textsuperscript{19}. Many therapeutic modalities such as laser photocoagulation\textsuperscript{16}, intravitreal bevacizumab injection\textsuperscript{5}, and photodynamic therapy (PDT) with verteporfin\textsuperscript{4,20} have been considered for resistant forms, but all of these procedures are invasive with specific complications.

Abnormal elevated levels of 24-hour urinary cortisol were detected in 50% of patients with acute or chronic CSCR in our study. It is compatible with Haimovici et al investigation that showed elevated 24-hours urinary cortisol levels in 50% of acute CSCR cases\textsuperscript{21}.

Bouzas et al reported that 5% of patients with endogenous hypercortisolism have experienced one or more episodes of CSCR and in all of them CSCR happened during the period of acute cushing disease while plasma cortisol concentrations were high. They suggested that glucocorticoid levels should be checked in patients with CSCR\textsuperscript{5}.

Additionally, exogenous corticosteroids via different routs of administration such as oral, intramuscular, intravenous, periocular and etc may promote or intensify the CSCR process\textsuperscript{10-14}. With higher doses of corticosteroids, the latency period will be shorter and recurrences will occur earlier\textsuperscript{22,23} and with discontinuation of the steroids, visual symptoms may be improved\textsuperscript{12,24,25}. Furthermore, many published studies; support a cause and effect relationship between corticosteroids and CSCR\textsuperscript{23,26,27}. The pathogenic mechanism by which corticosteroid excess is associated with the development of CSCR remains unclear\textsuperscript{1,14}. Several authors suggested several different explanations; including: increased capillary fragility and hyperpermeability\textsuperscript{2,28}, promotion of blood coagulation\textsuperscript{22,29}, inhibition of nitric oxide production\textsuperscript{30,31} and change in Bruch’s membrane structure\textsuperscript{32}.

Based on the causal role of corticosteroids in the development of CSCR, reduction of endogenous cortisol levels using corticosteroid antagonists such as RU486 (Mifepristone) or ketoconazole may be a useful method for the treatment of this disorder\textsuperscript{9,23}.

Ketoconazole is an anti-fungal agent which can inhibit the endogenous biosynthesis of cortisol and also can act as a glucocorticoid receptor antagonist\textsuperscript{9,16}; therefore ketoconazole is an established therapy in the treatment of cushing disease and some forms of prostate cancer\textsuperscript{9}. Based on the anti-glucocorticoid effects of ketoconazole, we used it for the treatment of CSCR.

In our study, 24-hour urinary cortisol levels were reduced after one month of treatment using oral ketoconazole (400 mg/day). Also, Meyerle et al showed that oral ketoconazole can decrease 24-hour urinary cortisol levels after 4 weeks of administration\textsuperscript{9}.

We have found significant anatomical improvement (Resolution of subretinal fluid with reduction of central macular thickness), resulting in significant recovery in VA in acute CSCR cases which may be due to the effect of ketoconazole on endogenous cortisol.

Golshahi et al treated 15 patients with acute CSCR using oral ketoconazole 200 mg/day. They showed VA improvement after 4 weeks, however, compared to the control group was not statistically significant\textsuperscript{33}. We have used higher doses of ketoconazole (400 mg/day) which in average resulted in improvement of BCVA from 0.56±0.2 at baseline to 0.84±0.2 after treatment. This improvement in BCVA is higher than visual outcomes in both treatment group (Increased BCVA from 0.6±0.2 to 0.7±0.2) and control group (Increased BCVA from 0.7±0.3 to 0.8±0.3) in Golshahi et al study\textsuperscript{33}. Therefore, our study showed that 400 mg/day of oral ketoconazole may be a safe and more effective dose for the treatment of acute CSCR. Patients with CSCR may experience spontaneous resolution of their symptoms and our results may be due to natural course of the disease, but the rapid recovery after treatment in our study may invoke the effect of ketoconazole administration.

Meyerle and coworkers treated 5 patients presenting chronic CSCR with ketoconazole
In this study, despite posttreatment reduction in 24-hour urinary cortisol, VA and lesion height remained unchanged. Although, our study showed that ketoconazole (400 mg/day) had no statistically significant effect on the BCVA improvement and central macular thickness reduction in patients with chronic CSCR, some patients experience complete or partial recovery. The coincidence of ketoconazole administration with improvement of long standing disease in some patients showed that ketoconazole may have a therapeutic role in the chronic course of this disease. Also, patients with higher baseline VA had more anatomical and functional recovery. This may be due to a milder disease process in them compared to others, and it means that earlier treatment in the course of the CSCR may result in more favorable outcomes.

**Conclusion**

In summary, oral ketoconazole (400 mg/day) may be a noninvasive, safe and effective therapeutic option for patients with acute CSCR and may alter the clinical course of chronic CSCR in some patients. However, the sample size in our study was small and the study was not randomized or controlled. Thus, a prospective, placebo controlled randomized clinical trial is necessary to demonstrate the therapeutic benefits of ketoconazole in CSCR.

**References**