INTERRVITREAL AVASTIN IN THE TREATMENT OF CENTRAL SEROUS CHORIORETINOPATHY

Vesna Dimovska Jordanova

University Eye Clinic
Faculty of Medicine, Skopje

Introduction: Central serous chorioretinopathy (CSCR) is usually a self-limiting disease that occurs due to the fluid accumulation underneath the retina, provoking distortion of vision or visual impairment. The condition typically affects 25-50 years old population and is 8-10 times more common in men compared with women.

The patients could be asymptomatic, or complaining on impaired or blurred vision, metamorphopsia, macropsia or dyschromatopsia. Clinical examination presents posterior neurosensory retinal detachment caused by leakage of fluid from the level of retinal pigment epithelium (RPE). Visual acuity varies in the range of 20/20 to 20/200.

The disease is commonly considered as stress-related, associated with corticosteroid exposure, obstructive sleep apnea syndrome and more often found in patients with “Type A” personalities. Fortunately, it resolves with good visual recovery in 80-90% within 6 months, but the recurrence could be observed in about 40% of the patients.

Diagnosis of the disease is based mostly on clinical examination on dilated pupil, Amsler - grid testing, Fluorescein angiography (FA) or Indocyanine Green Angiography (ICGA) and Optical Coherence Tomography (OCT).

So far, there is no “gold standard” treatment that should be recommended or that is widely approved and accepted regarding CSCR. In the majority of cases, there is no treatment needed and spontaneous visual recovery is very often. But, in recurrent or chronic CSCR, different treatment modalities have been used, such as focal laser photocoagulation, photodynamic therapy (PDT), anti-VEGF medications, or different kinds of pharmacologic treatment.

Material and Methods: The article presents case series of four patients with recurrent CSCR, treated with intravitreal injections of Bevacizumab (Avastin). All the patients had undergone assessment of best corrected visual acuity (BCVA), tonometry, slit-lamp fundus examination on dilated pupil with Volk 78 Dpt lens, Amsler-grid testing and OCT.

OCT was performed before, 1 month and 3 months following Bevacizumab injection.

Results: Although it is small case series, the results have shown improvement in visual acuity and resolution of neurosensory retinal detachment in three patients following intravitreal Bevacizumab. The last patient did not respond positively after the second injection, so the treatment was not continued. Control OCT at follow up has shown significant resolution of subretinal fluid and reducing of sensory retinal detachment.
**Conclusion**: The intravitreal injections of Bevacizumab in patients with recurrent central serous chorioretinopathy have shown favorable effects more addressing to the morphologic features (serous retinal detachment and central macular thickness) compared with best corrected visual acuity. Anti-VEGF treatment for recurrent CSCR at this point demonstrates beneficial outcome, but there is still lack of bigger clinical controlled randomized studies to confirm the initial encouraging data. *Acta Ophthalmologica* 2014;40(2):5-13.

**Key words**: central serous chorioretinopathy (CSCR), neurosensory retinal detachment, subretinal fluid, retinal pigment epithelium, anti-VEGF medications, Bevacizumab

---

**Introduction**

Central Serous Chorioretinopathy (CSCR) is an idiopathic and usually a self-limiting disease that occurs due to the subretinal fluid accumulation in the macula provoking distortion of vision or visual impairment. The condition typically affects 25-50 years old population and is 8-10 times more common in men compared with women. (1) Patients may be asymptomatic, or have symptoms as decreased or blurred vision, distortion of objects (metamorphopsia), small image perception (macropsia) and color vision impairment (dyschromatopsia). Visual acuity can vary in range of 20/20-20/200.

The exact etiology of the disease has not been elucidated yet, but the condition could be triggered by stressor of corticosteroid exposure. It could be related to obstructive sleep-apnea, “type A” personality individuals, phosphodiesterase inhibitor use, higher prevalence of migraine-like headaches or psychiatric conditions. It is more common in Caucasians, Hispanics and Asians. (2) Some observations based on Indocyanine green angiography (ICGA) suggest that CSCR is primarily a chorioidopathy, but there are still controversial opinions whether the primary underlying pathology is at the level of choroid, the retinal pigment epithelium, or both. (2)

Evidence emerging from some researches indicate that the disease pathophysiology in CSCR is more diffuse and shows bilateral retinochoroidal dysfunction, even when the disease is clinically affecting only one eye. It is believed that abnormalities in choroidal circulation are altering overlying retinal pigment epithelium, making it dysfunctional, causing development of a serous retinal detachment. (3)

Clinically, CSCR is characterized by avascular focal leakage through the retinal pigment epithelium (RPE), resulting in serous detachment of the neurosensory retina. In majority of patients it is a unilateral condition, but up to 18% of the cases could be bilateral. (2)

**Natural history**

In general, CSCR has a good prognosis regarding final visual acuity that is mostly restored following spontaneous visual recovery. Majority of eyes have stable visual acuity of 20/30 to 20/40. The neurosensory retinal detachment usually resolves within three to four months. Still, up to 20 % of the cases may have persistent serous macular detachment with some extent of visual impairment and subjective symptoms as micropsia or dyschromatopsia. The rate of recurrence is registered in one-third to one-half of the patients with CSCR. If subretinal fluid is not resolved within three months, the condition is defined as chronic CSCR with consideration for further treatment. (1, 2)

Lower final visual acuity is associated with persistent or recurrent foveal detachments, CNV, subretinal fibrosis, subfoveal RPE atrophy, multiple sites of leakage, larger pigment epithelium detachments, or cystoid macular edema.

**Diagnosing of CSCR**

Fundus examaination on dilated pupil with slit lamp or indirect opthalmoscopy is essential and basic examination for recognizing the clinical features of CSCR. Typical findings include a round, well-delineated, shallow, serous macular neurosensory detachment, often surrounded with a halo light reflex. If the fovea is affected, the normal foveal light reflex is absent and instead, a prominent yellow-colored dot could be present within the foveal region. Small, round, yellow or gray serous RPE detachments (PEDs) could be visualized.
Figure 1. (1a, 1b). Central Serous Chorioretinopathy

Figure 2. Typical “smokestack” appearance on FA in CSCR

Fluorescein angiography (FA) is often performed for confirming the diagnosis of CSCR and excluding other similar conditions. The angiogram demonstrates expanding site of fluorescein leakage with late pooling into the serous detachment. Single or multiple discrete leakage points could be observed, followed by later dye distribution throughout the subretinal fluid and visualization of a retinal pigment epithelium detachment. The classic “smokestack” appearance is seen in less than 20% of the cases. (2)

Figure 3. Chronic CSCR

Indocyanine green angiography (ICGA) could show focal delays and hyperpermeability in the choroidal circulation in patients with CSCR. ICGA is beneficial due to its ability to identify and differentiate CSCR towards AMD or polyoidal choroidal vasculopathy.

Optical Coherence Tomography, as novel and imaging diagnostic tool, should not be treated as a substitution to FA. However, one has to admit that numerous advantages of OCT (noninvasive, no dye needed, repeatable without any side effects or complications) made this method irreplaceable not only in diagnosing, but also in monitoring the evolution and treatment effects in CSCR. OCT superiorly demonstrates the amount of subretinal fluid, that is often associated with a focal pigment epithelium detachment. Data emerging from studies performed with enhanced-depth imaging spectral domain OCT have shown increased subfoveal choroidal thickness in some patients with CSCR compared to normal eyes. (1)

Figure 4. Massive sensory retinal detachment associated with RPE defect

Treatment modalities

Central Serous Chorioretinopathy is usually a self-limiting disease with spontaneous visual and morphologic recovery within 3 months, resulting in overall good final visual acuity.
Never the less, the rate of recurrences is estimated to be about 50% during the first year. These recurrences or chronic neurosensory detachments may provoke RPE atrophy or hypertrophy with significant impairment of visual function. Therefore, observation is considered and recommended as the first line approach in newly diagnosed cases with less than 3 months duration.

So far, there is no “gold standard” treatment modality that is mostly appreciated and accepted regarding CSCR. Different treatment options that could be taken into account are mostly referring to chronic CSCR, recurrent CSCR, single CSCR attack of more than 3 months duration, and cases of fellow eye with permanent visual loss due to the previous episode of CSCR.

Historically, different therapeutic options have been used in the treatment of CSCR, such as: laser photocoagulation, photodynamic therapy (PDT), pharmacologic agents, and most recently, intravitreal instillation of anti-VEGF medications. It has to be emphasized, that none of past and current treatment options has FDA approval as first line therapy for difficult cases of CSCR.

Laser photocoagulation

Several treatments based on different laser wavelengths have been applied to the site of leakage, in order to fasten the resolution of subretinal fluid and sensory retinal detachment. In this manner was used ruby laser, xenon laser, krypton laser, argon laser and finally nowadays micropulse diode laser photocoagulation. Although a few studies have reported encouraging results using micro pulse diode laser (minimized retinal damage and indication in eyes with focal leakage), the data analysis has confirmed that focal laser photocoagulation does not influence the final visual acuity and does not reduce the rate of recurrence.(1)

Therefore, focal laser photocoagulation is considered as an effective treatment mode in acute CSCR with clearly defined focal leakage observed on FA, that is not subfoveal or juxtafoveal.

Having in mind laser photocoagulation being a destructive procedure that could lead to serious side effects (permanent scotoma, laser scar enlargement, laser induced CNV), it is generally recommended that the treatment should be performed in selective cases, as:

- A site of leakage away from the foveal center
- A professional necessity for prompt visual recovery

Photodynamic therapy

Photodynamic therapy (PDT) targets the choroidal circulation more directly and has ability to be used in cases with subfoveal and/or multifocal points of leakage. It is believed that PDT works in CSCR by inducing choroidal hypoperfusion, with vascular narrowing and remodeling to negate choroidal hyperpermeability, which is consistent finding in cases with CSCR. Other authors are suggesting a mechanism of PDT tightening the blood-retinal barrier.(2)

However, PDT does not have FDA approval for the treatment of CSCR, bearing in mind the side effects, including photosensitivity to intravenous dye.

Some recent studies have demonstrated the use of half-fluence and half-dose PDT in acute and chronic CSCR, trying to maintain the efficacy of the treatment while minimizing the risks.

Pharmacologic treatment

A few smaller studies have reported mixed results from a variety of systemic medications used for the treatment of CSCR. Treatment efforts have been made using carbonic anhydrate inhibitors, adrenergic receptor antagonists, steroid hormone antagonists, aspirin, etc. Special concern should be pointed towards the use of systemic corticosteroids. If it is not contraindicated regarding the primary disease, these medications should be discontinued in patients with active CSCR. Pharmacologic treatment for CSCR still remains unsatisfactory and needs future improvement.

Anti-VEGF agents

Applying anti-VEGF medications in patients with CSCR is novel treatment modality with promising initial results. This kind of treatment is recommended for chronic and recurrent CSCR.

There is still lack of direct evidence that Vascular Endothelial Growth Factor is somehow included in the pathogenesis of CSCR. But, the presumed role of increased choroidal hyperpermeability as one of the main underlying mechanisms in CSCR has induced the anti-VEGF medications as possible treatment options for this condition.
Anti-VEGF drugs have ability to provide a number of effects that are theoretically beneficial in CSCR, such as the up-regulation of tight junctions between endothelial cells and reduction of vascular fenestrations. The suggested mechanism of action is that VEGF levels in the aqueous humor of patients with chronic CSCR may be elevated compared with normal eyes. Case studies reporting the results of intravitreal instillation of anti-VEGF medications in patients with persistent or chronic CSCR have shown improvement in visual acuity, resolution of neurosensory detachments and decreased RPE leakage on FA. No severe side effects or adverse events were noted.(1,3,4,5).

Chronic CSCR disease is a term that defines cases with diffuse RPE changes without evident detachment in most patients. Despite this explanation, ophthalmologists are often facing difficulties to make clinical difference between chronic disease and recurrent episode of CSCR. Some clinicians tend to identify chronic CSCR as serous macular elevation detected biomicroscopically or by OCT, that is associated with RPE atrophic areas and subtle leaks.(3)

Chronic CSCR is defined as persistent symptoms of the disease for more than 6 months, while recurrent CSCR as a condition with more than single episode in a patient.

So far, the studies reporting anti-VEGF treatment for CSCR are presenting the results using intravitreal Bevacizumab (Avastin, Genentech/Roche), that is approved by Food and Drug Administration Agency for the treatment of colorectal cancer. Avastin is used “off label” in the treatment of other ocular diseases (AMD, cystoid macular edema, proliferative diabetic retinopathy, macular edema following retinal vein occlusions, retinopathy of prematurity).

Bevacizumab is a recombinant humanized full-length monoclonal antibody of VEGF that penetrates the retina and is transported into the photoreceptor outer segments, RPE and choroid after applied intravitreal injections.

The mechanism of action of intravitreal Bevacizumab is unknown, but might involve effects on choroidal vascular hyperpermeability.(6)

In the following text we are presenting a case series of four patients with recurrent CSCR that were treated with intravitreal Bevacizumab.

**Case series**

We are reporting case series of four male patients, age 45-55 years, that have suffered from recurrent CSCR. Due to the recurrent history of the disease, they were treated with intravitreal injections of Bevacizumab (Avastin). The number of applied injections varied from 1-3. One of them was also treated with argon grid focal laser photocoagulation 10 years ago.

The patients were examined for best corrected visual acuity (BCVA) on Snellen’s chart, tonometry, clinical evaluation on dilated pupil with Volk lens of 78 Dpt, Optical Coherence Tomography (Topcon 3D 2000) and Fluorescein angiography in two cases (others had previous hypersensitivity to Fluorescein dye). The procedures were performed before, 1 months and 3 months following intravitreal injections. Postoperative follow up included clinical examination the next day, after 1, 2 weeks and one month, whereas control OCT was made at one and three months after the injections. Special attention was paid to potential adverse events, including increased intraocular pressure, vitreal opacities or haemorrhage, cataract progression, retinal detachment and endophthalmitis.

The main study endpoints were changes in BCVA and resolution of subretinal fluid and neurosensory retinal detachment assessed on repeated OCT.

Treatment was performed by standard protocol for intravitreal injections of Avastin (sterile conditions in operating room with Avastin single dose of 1.25mg/0.05ml).The patients were advised to apply topical antibiotics in the injected eye four times a day during 5-7 days.

Post-treatment results have shown slight improvement in BCVA on Snellen’s chart in three patients, but the subretinal fluid resolution on OCT was more pronounced than the improvement in BCVA. In three patients control OCT has shown complete resolution of subretinal fluid, while in the last patient there was no beneficial effect after 2 injections of Avastin and the future treatment was discontinued.

Besides the morphologic improvement on OCT, patients had reduction of subjective symptoms (decrease of blurred vision and metamorphopsia).
Patient No 1.

Fig. 5 A: Right - OCT before IVB
Fig. 5 B: Left - OCT 3 months following single injection of IVB

Patient No 2.

Fig. 6 A: Right - OCT before IVB
Fig. 6 B: Left - OCT 3 months following 2 injections of IVB
Discussion

A number of studies performed on selective patients with chronic or recurrent CSCR treated with intravitreal injections of Bevacizumab, are reporting encouraging results, without any serious side effects. Most studies reported that intravitreal Bevacizumab (IVB) injections may be beneficial and effective in terms of improving visual acuity and reducing central macular thickness without significant complications.(7)

But, there is still missing a large randomized controlled clinical trials investigating effects of intravitreal Bevacizumab in patients with CSCR. The majority of studies on IVB in CSCR conducted so far has been interventional case series, with certain limitations, mostly regarding small samples, short follow up and heterogeneity in inclusion and exclusion criteria.

Although our reported case series has serious limitations regarding the small number of patients, the results of the treatment of recurrent CSCR with intravitreal Bevacizumab (IVB) were consistent with the similar studies consulted in the literature. (3,4,5,6,8,9). The most important outcome was the resolution of subretinal fluid and sensory retinal detachment. Such an improvement in anatomic, respectively morphologic features was documented by control OCT after injections.

The anatomic and functional improvement observed in other conducted studies following intravitreal Bevacizumab injections suggest that VEGF may be involved in fluid leakage in patients with CSCR. This is consistent with some previous studies emphasizing the efficacy of Bevacizumab in the treatment of different forms of CSCR and resolution of subretinal fluid due to decreased choroidal vascular hyperpermeability that occurs after IVB injection.(3,6) This is supported by the presumption that choroidal vascular hyperpermeability is considered to be a fundamental mechanism in both acute and chronic CSCR, and the current treatment concept, such as PDT or IVB, is focused on modulating hyperpermeability of choroid.(7)

It is believed that during the acute course of the disease, there is disrupted integrity of RPE resulting in occurrence of its detachment, associated with focal leakage. This mechanical alteration of RPE architecture (“blowout”) is responsible for the development of serous detachment.(10)

Some researchers are suggesting IVB injections to be applied as primary (initial) treatment in persistent CSCR on selective cases characterized with better visual acuity, smaller lesions and thicker choroid at baseline.(8)

Conclusions

Although it is well known that idiopathic central serous chorioretinopathy is most often self-limiting disease with good final prognosis, cases with chronic and recurrent CSCR are not only individual problem of the affected patients, but also a challenging effort for the ophthalmologists.

There is still no evidence based “gold standard” treatment, and currently a variety of treatment modalities have been used. Majority of patients will return to baseline without any therapy, but still, a number of patients would need further treatment.

Different modalities of pharmacologic treatment are still investigational and the results remain to be reported in the future.

Photodynamic therapy has been considered useful option for chronic CSCR, but there is still serious concern regarding potential adverse events, including chorioretinal atrophy.

Anti-VEGF agents, mostly applied as intravitreal Bevacizumab injections, may represent a new, promising treatment option for selected cases with chronic or recurrent CSCR. This finding, that was confirmed in our small case series, is consistent with previously published studies investigating such cases. Data emerging from most of the conducted studies suggest a possible role of anti-VEGF agents in the treatment of CSCR, pointing out that intravitreal injections of Bevacizumab were associated with visual improvement and reduced neurosensory retinal detachment without any serious adverse effects.

But, on the other hand, prospective studies using anti-VEGF medications in CSCR have demonstrated inconsistent results. Cumulative base of evidence has not provided consistent, convincing and sustained clinically significant benefits for the patients.

Finally, predominant opinion is that intravitreal injections of Bevacizumab as treatment option in CSCR should be assessed objectively through conducting controlled randomized clinical trials, embracing large number of patients with longer follow up period. Such an approach would strongly support and evaluate the potential efficacy and safety of Bevacizumab, succeeding to determine the ideal protocol for this promising new treatment at this moment.
References

2. Shuler RK and Mruthyunjaya P. Diagnosing and managing central serous choriotiretinopathy. Retina Today, Jan/Feb 2010
5. Avastin effective for persistent central serous choriotiretinopathy. My Vision Tests News Archive, Feb 2010

INTRAVITREALNI AVASTIN U LEČENJU CENTRALNE SEROZNE HORIORETINOPATIJE

Vesna Dimovska Jordanova
Univerzitetska očna klinika
Medicinski fakultet, Skopje


Dijagonzo bolesti se uglavnom bazira na kliničkom pregledu kroz proširene zenice, Amslerovom testu, fluoresceinskoi angiografiji (FA) ili angiografiji indocijaninskim zelenilom (ICGA) i optičkoj koherentnoj tomografiji (OCT).

Za sada ne postoji “zlatni standard” u lečenju ove bolesti koji bi se preporučio, ili koji je odobren i široko prihvaćen. U većini slučajeva lečenje nije ni potrebno i često dolazi do spontanog vraćanja vida. Ali, kod recidiva ili hronične CSCR se koriste različiti modaliteti lečenja, kao što su fokalna laserska fotokoagulacija, fotodinamska terapija (PDT), anti-VEGF lekovi, ili razne vrste farmakoloških terapija.

Materijal i metode: Ovaj rad predstavlja prikaz slučajeva četiri pacijenta sa recidivnom CSCR, lećenih intravitrealnim injekcijama Bevacizumab (Avastin). Kod svih pacijenata su urađene procene najbolje korigovane vidne oštrine (BCVA), tonometrija, pregled očnog dna slit-lampom kroz proširenu zenicu, korišćenjem Volk 78 Dpt lens, Amslerovog mrežnog testa i OCT. OCT je urađen pre davanja injekcije Bevacizumab, kao i nakon jednog i tri meseca.

Rezultati: Iako se radi o malom broju slučajeva, rezultati su pokazali poboljšanje vidne oštrine, nestajanje ablacije neurosenzorne retine kod tri pacijenta...
nakon što je intravitrealno primenjen Bevacizumab. Poslednji pacijent nije pozitivno reagovao nakon druge injekcije, te je tretman prekinut. Kontrolni pregled optičkom koherentnom tomografijom (OCT) je u toku praćenja pokazao u značajnoj meri nestajanje subretinalne tečnosti i smanjenje senzorne retinalne ablacije.

**Zaključak:** Intravitrealne injekcije Bevacizumab su kod pacijenata sa recidivnom centralnom seroznom horioretinopatijom pokazale povoljne efekte više u smislu morfoloških karakteristika (serozna ablacija retine i centralno makularno zadebljanje) u poređenju sa najbolje korigovanim vidnom oštrim.


**Ključne reči:** centralna serozna horioretinopatija (CSCR), neurosenzorna ablacija retine, subretinalna tečnost, retinalni pigmentni epitel, anti-VEGF lekovi, Bevacizumab

**Kontakt:** Vesna Dimovska Jordanova  
“Cedomir Minderovic” 30, 1000 Skopje, Macedonia  
e-mail : vesnajdimovska@gmail.com