Anti-VEGF injection for treatment of chronic central serous choridopathy: A case report
Salwa Attia
Department of Ophthalmology, GMC Hospital, Ajman, UAE

ABSTRACT
Objective: Central Serous Choridopathy (CSC) in an eye disease which causes visual impairment, often temporary, usually in one eye, mostly affects males in the age group 20 to 50 but which may also affect women. When the disorder is active it is characterized by leakage of fluid under the retina, re-accumulate under the central macula. This results in blurred vision with metamorphopsia. A blurred or gray spot in the central visual field is common when the retina is detached. Reduced visual acuity may persist after the fluid has disappeared.

Material and Methods: A 36 years old male was presented to GMC Ophthalmology clinic with history of poor vision in his left eye since 7 years which was diagnosed as CSC at that time and general steroid treatment was given in dose of 80mg tabs daily for 2 weeks with no improvement and vision was stayed very poor in left eye since that time. On examination vision in left eye was 0.3 aided and no improvement by pinhole. OCT shows fusiform shaped space of sub macular oedema which was diagnosed by us as Lt chronic central serous retinopathy, Decision was made to inject him Intravitreal Anti-VEGF in his left eye.OCT, IOP and vision estimation was made before injection and three days after injection, then weekly for one month, monthly for 6 months.

Results: OCT after 3 days from injection shows complete absorption of the submacular fluid with improvement of vision more than 4 lines.

Conclusion: Intravitreal Anti-VEGF proved to be an easy, safe and effective new method of CSC treatment even in chronic cases and comes to be superior to conventional methods of treatment like:
- Laser photo coagulation
- Transpupillary thermotherapy
- Photodynamic therapy
And this gives new indication added to the indications of use of intravitreal Anti-VFGF.

Keywords: central serous choridopathy (CSC), anti-VEGF

INTRODUCTION
Central serous chorioretinopathy (CSCR) is an idiopathic disorder characterized by neuroepithelial serous detachment, with or without concomitant pigment epithelium detachment (PED) and decompensated retinal pigment epithelium (RPE) associated with one or more focal active leakage sites (ALS) at the level of the RPE (‘smoke-stack’ on fluorescein angiography (FA)). The underlying pathogenesis of CSCR is not thoroughly understood.

Hypotheses on the pathogenesis of CSCR have ranged from a basic alteration in the choroid to an involvement of the retinal pigment epithelium (RPE). Starting from evidence that affected subjects often present a personality prone to stress with altered pituitary–hypothalamic axis response (HPA) and they have higher levels of serum and urinary cortisol and catecholamines than healthy subjects, a cascade of events that may lead to CSCR through hypercoagulability and augmented platelet aggregation.

This disease is common in males between 20 to 45 years of age. CSCR is more common in Caucasians, Hispanics and Asians, and less common in those of African descent. Choroidal circulation abnormalities (most likely choriocapillaris) precede disintegration of the RPE.

The symptoms of CSCR are blurred vision, a dark spot in the center of the visual field; micropsia and metamorphopsia are all caused by anterior displacement of
the retinal plane after subretinal effusion due to porous RPE. Within 3 months resolution of CSC will happen in more than 50% of patients, with recovery of visual acuity (VA) despite some pigment epithelium scarring.

Optical coherence tomography (OCT) examinations often reveal several PEDs that, when chronic, are associated with subretinal accumulation of fibrin, lipids, choriocapillaris atrophy, and choroidal neovascularization.

A sectorial hypoperfusion will lead to vascular bed reduction due to vasoconstriction and this to capillary occlusion, accordingly increasing in the endoluminal pressure perfusion in the surrounding healthy vascular bed.

The increased endoluminal pressure will lead to leakage of serum and small molecules in the stroma causing a further vascular tamponade. Since choroidal blood flow can be described by Hagen–Poiseuille’s law ($\Delta P = 8 \mu LQ/\pi r^4$), it follows that small differences in total radius of vascular bed induce a high increase in endovascular pressure with fluid extravasation and, in the same direction, a variation in viscosity ($\mu$) determines a modification of choriocapillaris hemodynamics.

The affinity of the disease for the macular area is due to the particular organization of the choriocapillaris with a closer meshwork than the peripheral choroid.

The term acute CSC usually refers to the self-limiting CSC that resolves spontaneously over a few months without any treatment and minimal residual changes on imaging. Chronic CSC, meaning a serous macular elevation, visible biomicroscopically or detected by OCT, which is associated with RPE atrophic areas. The main difference between chronic and acute disease is the fact that chronic disease has widespread pigment epithelial changes without detachment, whereas in acute disease there is focal pigment epithelial abnormality and marked detachment.

Photoreceptor atrophy in the fovea occurs after four months. Attenuation of the foveal photoreceptor layer is associated with permanent visual loss. Foveal photoreceptors damage which happens with chronic CSS signs could be considered as the high risk group of treatment should be applied.

Only we consider considered treatment in recurrent chronic CSC or a single CSC episode, of greater than 3 months duration, with some signs of chronic CSC. Usually visual loss in the fellow eye caused due to similar procedure, in this case we must treat even in absence of chronic CSC.

Patients usually present with a disturbance in central vision, a blind spot in the central field, metamorphopsia. "ons to the retinal pigment epithelium. In the acute stage, there is an overlying elevation of the neurosensory retina. If the

Figure 1: Previous Pharmacological and other Treatment Suggestions
subretinal fluid does not involve the central of macula or foveal region they will not feel any symptoms. If the neurosensory part of retina is displaced or become away from its source of nutrition, which is the choroidal circulation.

Corticosteroids was the treatment of choice in CSC for several years either by the oral route or by local subconjunctivally, but are no longer recommended as knowledge of CSC pathogenesis has evolved\textsuperscript{12-14}.

Adrenocorticotropic hormone\textsuperscript{15}, anti-inflammatory drugs\textsuperscript{16}, retrobulbar esmolol injections\textsuperscript{17}, subconjunctival injections of milk, albumin and salt solutions, anti-syphilitic and anti-tubercular drugs, insulin-free pancreatic extract, and thyroid extract have all also been suggested in the past\textsuperscript{18}. The use of the above agents was not proven to be effective by any clinical trials\textsuperscript{19}.

Carbonic anhydrase inhibitors are also tried for treating CSC with short-term encouraging results but no evidence of long-term benefit\textsuperscript{20}.

**Treatment options for CSC**

- The Use of Argon Laser Photocoagulation (Focal photocoagulation of the leakage sites)\textsuperscript{21-24}. A reduction in CSC recurrences and shortening of the duration of detachment with direct laser photocoagulation compared with sham or indirect (away from the site of leakage)\textsuperscript{25,26}.
- Untreated eyes were 3.3 times more prone to develop a recurrence than treated eyes.

However, if the area of leakage is subfoveal or juxtafoveal, photocoagulation may induce secondary choroidal neovascularisation (CNV) and/or of damage foveal photoreceptors\textsuperscript{27}. Therefore other treatment options appear safer.

Transpupillary Thermotherapy TTT in chronic CSC, which resulted in the resolution of CSC with subfoveal angiographic leaks and marked improvement in visual outcome. Photodynamic Treatment with Verteoporfirin has recently been utilized to treat ICSC. Both have an occlusive effect on CNV and also affect normal choroidal perfusion\textsuperscript{28}.

Both Fluorescein and ICG-A-guided PDT have been recommended for treatment of ICSC\textsuperscript{29}.

PDT acts by both decreasing choroidal hyperpermeability and by tightening the blood–retinal barrier at the level of the RPE\textsuperscript{30}.

Choroidal hypoperfusion, can also lead to some complications, like if conventional PDT is performed, according to the Treatment of age-related macular degeneration three cases of abrupt visual loss due to severe choroidalischaemia after using standard PDT in CSC patients\textsuperscript{31,32}. RPE atrophy, juxtafoveal CNV, and transient reduction in macular function\textsuperscript{33,34}.

A hypothesis that VEGF antibodies could reduce choroidalhyperpermeability and choriocapillarisischemaia associated with CSC\textsuperscript{35} resulted in treatment

![Figure 2: (a) OCT image of a CSC patient before intravitreal injection of (ranibizumab) showing a large amount of subretinal fluid involving the fovea. (b) OCT image of the same patient 3 months after treatment with intravitreal injection of (ranibizumab) showing complete resolution of subretinal fluid.](image-url)
of acute and chronic forms of CSC with intravitreal injection of (ranibizumab and bevacizumab (Avastin))\textsuperscript{36-39}.

Larger, controlled trials are still needed to evaluate the efficacy and safety of anti-VEGF agents for this indication.

Micropulse Diode Laser Photocoagulation (810 nm) has recently been assessed for the treatment of chronic CSC\textsuperscript{40-45}. To avoid retinal damage, caused by conventional laser photocoagulation. It has been used in chronic CSC, in eyes with either well-defined leaking sites or diffuse leakage and proved to be safe from treatment of Chronic CSC.

Subthreshold micropulse diode laser photocoagulation therefore appears to be a safe form of treatment in chronic CSC. Results however are not superior to PDT. Furthermore, micropulse diode laser photocoagulation seems unsuitable for diffuse leakage and diffuse RPE decompensation. These are frequent findings in chronic CSC cases.

**MATERIALS & METHODS**

**History**

A 36 years old male was presented to GMC Ophthalmology clinic with history of drop of vision in his left eye since 7 years which was diagnosed at that time as acute CSC.

General steroid treatment was given at that time in the form of oral tabs in a dose of 80mg per day for 2 weeks. No improvement was achieved at that time and vision stayed very poor in left eye since that time. On examination vision in left eye was 0.3 non-aided and no improvement with glasses, vision in Rt eye was 0.9 non-aided.

Our diagnosis started with a dilated examination of the retina, followed with confirmation by optical coherence tomography and fluorescein angiography. The old angiography showed one fluorescent spot with fluid leakage which appeared in a “classic” smoke stack shape. OCT shows fusiform shaped space of submacular oedema which was diagnosed by us as Lt chronic central serous chorio retinopathy.

No history of use, of any exogenous corticosteroids (oral, topical, intranasal, and invasive) in the 6 months prior to the study, as well as no diabetic retinopathy, no uveitis, any hereditary retinal/macular disease, or history of intraocular surgery.

Chronic CSC was defined as RPE leakage on FA persisting at least 3 months, with or without areas of diffuse RPE decompensation and corresponding subretinal fluid accumulation evidenced at OCT.

Decision was made to inject him Intravitreal Anti-VEGF in his left eye. OCT, IOP and vision estimation was made before injection and three days after injection, then every week for one month, then monthly for 6months.

Patient ophthalmic examination, at baseline and at 6 weeks, 6 and 10 months after treatment, included slit-lamp biomicroscopy, indirect ophthalmoscopy, best-corrected visual acuity (BCVA), Amsler grid screening, Central Macular Thickness (CMT) with OCT, and FA after initial treatment.

Applanation tonometry Keeler 2401-P-2700 was used to measure the intraocular pressure (IOP). The CMT at the foveola was assessed by OCT in the automated mode (line and retinal thickness map mode, Model 3D.OCT.2000 (FA plus), TOPCON, Japan ). FA was done with the use of (FA plus camera, TOPCON, Japan) and performed with 5 cc of 10% fluorescein (Fluorescein, Altaire pharmaceuticals, INC, Aquebogue NY).

Written informed consent was taken from the patient, clearly explaining all potential risks and possible benefits of treatment with intravitreal injections of RBZ.

The patient was treated according to the standard operating regulations of the hospital, with antiseptic conjunctival flush using 3 % Povidone iodine before the injection. Sterile marker was used to mark the sclera at the 4mm post-limbal superior temporal sector. LUCENTIS® (ranibizumab injection) designed for intraocular use.
**TREATMENT CRITERIA**

Chronic CSC requires a tailored and delicate treatment approach that addresses the sites of leakage and the state of the RPE. Distinguish between ‘acute CSC’ and ‘chronic CSC’ was not really done in literature, although there is a general belief that such a distinction would correlate with the long-term visual prognosis as well as the decision of whether to treat or wait and when to start treatment.

The treatment rationale is based on the ability to decrease fluid from retina’s ALS because the pharmacodynamics and pharmacological pathway of RBZ in CSC is poorly understood. The drug penetrates all retinal layers including the RPE, with the complications, such as choriocapillaris damage, RPE atrophy, or ganglion cell damage after long-term successive treatment. In spite of this complication absolute and migrating scotoma associated with the current treatment options, conventional thermal laser photocoagulation or photodynamic therapy (PDT), both SDM photocoagulation and intravitreal injections of RBZ offer a better modality of treatment in term of its clinical effectiveness and intra/postoperative safety profile and, in our view, may potentially represent better treatment modalities.

Both ranibizumab and bevacizumab, which are derived from the same parent molecule, inhibit all isoforms of VEGF. However, molecular and pharmacologic properties of these agents differ in several aspects. In an experimental animal model, ranibizumab has been shown to penetrate the choroid rapidly after an intravitreal injection. Bevacizumab is a three times larger molecule. Investigations, however, have proven the presence of bevacizumab throughout the neural retina, in the subretinal space and choriocapillaris within 24 hours of Intravitreal injection.

In our case, chronic CSC (7 years) was successfully treated with 2.5 mg of single dose intravitreal ranibizumab injection.

One week later, subretinal fluid was completely resolved and the vision improved to 20/25 and remained stable within one year.

OCT after 10 days from injection shows complete absorption of the submacular fluid with improvement of vision more than 4 lines.

**DISCUSSION**

CSC is characterized by idiopathic serous detachment of the neurosensory retina. There are three theories on CSC pathogenesis:

1. Disorder of the outer BRB, which leads to choroidal vascular hyperpermeability.
2. Dysfunction of the RPE with a reversal of liquid transport.
3. Damage of RPE due to shedding of outer photoreceptor segments with a primary intact BRB.

Clinical improvement in VA can only be achieved with resolution of subretinal fluid. The state of the RPE is crucial in the pathophysiology and prognosis of the disease itself, and should be taken into consideration for active treatment.

Focal laser treatment, the oldest and still questionable therapeutic option is only effective for the coagulation of the ALS on FA. Damage to the neurosensory retina by the thermal effect of laser make it only possible in treating extrafoveal sites with putting in consideration to minimize the lazer induced absolute scotomata. Contrast sensitivity loss, accidental foveal damage, retinal distortion, rupture of Bruch’s membrane, and choroidal neovascularization are also main complication of thermal effect of laser.

PDT is used when the RPE lesion is juxta-foveal or subfoveal. PDT counteracts the choroidal hyperperfusion which is the hallmark of CSC development due to local choroidal thrombosis.

Studies have shown that intravitreal anti-VEGF agents effectively resorb subretinal fluid in up to 80% of the cases.

One of the most thorough studies on
the intravitreal injection of BCZ treatment in CSC to date which compared it with SDM photocoagulation, intravitreal BCZ seems to reduce subretinal fluid faster, but requires frequent reinjections, regardless of the dosage, they used 1.25 mg of BCZ. In as described by Inoue et al., whereas some groups used 5 mg.

CSC, unlike in exudative AMD, intravitreal anti-VEGF injections were not associated with long-term damage to the RPE, the choriocapillaris, or the ganglion cells. However, CSC patients are usually younger, and ongoing intravitreal injections might not be a sustainable therapy.

CONCLUSION

Intravitreal Anti-VEGF proved to be an easy, safe and effective new method of CSC treatment even in chronic cases and comes to be superior to conventional methods of treatment like:
- Laser photo coagulation
- Transpupillary thermotherapy
- Photodynamic therapy

And this gives new indication added to the indications of use of intravitreal Anti-VFGF.

REFERENCES


