

The Safer Method of Sub-Tenon's Bevacizumab Injection with Central Serous Chorioretinopathy: A Non-invasive Evaluation by Series of Optic Coherence Tomography

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Abstract: Purpose: To evaluate the outcome of patients with central serous chorioretinopathy (CSCR) after deep sub-tenon bevacizumab injection by the noninvasive evaluation by optic coherence tomography (OCT). **Methods:** Three patients having CSCR with moderate to severe vision loss were treated with at least two time of sub-tenon bevacizumab injection (0.3 ml). All the patients underwent the complete examinations at the baseline and follow-up visits. This ocular evaluation included the bare and best-corrected visual acuity (by Snellen chart), fundus biomicroscopy and OCT in each visit. **Results:** The follow-up point ranged between 2 and 6 months. Improvement of vision was observed, and they all had better visual acuity. The serous retinal detachment improved in all eyes and no complications were noted. The detailed findings could be easily explained and monitored by OCT. **Conclusion:** Deeper sub-tenon bevacizumab injection was safer and also effective in treatment of CSCR. It can induce regression of edema from serous detachment, decrease the choroidal hyper-permeability and enhance the absorption of subretinal fluid. Besides, the use of series of OCT may help us more easily to detect the posterior pole of fundus and the prognosis after bevacizumab injection. The ophthalmologists also explain to the patients and their families by detailed and simply known tomographic pictures.

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1. Introduction

Central serous chorioretinopathy (CSCR) is characterized by serous retinal detachment, retinal pigment epithelial (RPE) detachment or dysfunction, and choroidal hyper-permeability. It is commonly seen in young and middle-age men. Although the pathogenesis of this disease may be the effect of glucocorticoid and adrenergic hormones on the RPE and choroid [1,2,3]. Patients often develop symptomatic central scotomas in the macula or the para-macular region [4,5]. Although it may spontaneously improved within 2 to 3 month [3,5], however, chronic CSCR occurs in approximately 5% of patients which is often bilateral, multifocal, recurrent and may be associated with sub-retinal fibrin formation within

the blister [27]. The visual acuity in some cases may be affected and harmed forever in bullous retinal detachment with residual sub-macular fibrosis [6,7]. Some patients also would develop into chronic CSCR with poor prognosis which is characterized by the widespread of distribution of small pigment epithelial detachments associated with areas of RPE atrophy and extensive pigmentary changes [8,9,10]. In rare cases, recurrent detachments and RPE changes can lead to permanent loss of vision [6,9]. Now many methods were used to control and treat the patients with CSCR such as higher doses of systemic steroids [11], Ketoconazole [58], low dose of aspirin [28], argon laser photocoagulation (to seal the leaking points in the RPE) [11], Photodynamic therapy (PDT)

guided by ICG angiography [12] , performed according to the TPA study protocol to resolve macular detachment and preserve the vision [13,14,15] and even need surgical intervention for sub-retinal fluid drainage [11] . However, the various side effects and weak points were noted (for example, steroid may impact on the leakage from blood vessels, laser photocoagulation may increase the risk of CNV, the medical effect of PDT is very slow). Therefore, many researchers focused on the newer methods and drugs in recent years.

Bevacizumab (Avastin) is now approved by Food and Drug Administration (FDA) as an adjunct for the treatment of metastatic colorectal cancer and metastatic breast cancer in USA [16] . It is a monoclonal antibody that binds all iso-forms of vascular endothelial growth factor A (VEGF-A). Avastin plays a important role in the inhibitor of angiogenesis, and has also been used effectively in the treatment of neovascular ARMD (age-related macular degeneration) in the world [17] . Until now, intravitreal injection of anti-VEGF agents has been reported effectively in inducing the regression of new vessels in proliferative diabetic retinopathy with vitreous hemorrhage [18] , neo-vascular glaucoma [19] , and sub-macular hemorrhage [20,21] . Besides, the use of Avastin to treat the patients with CSCR was accepted gradually recently [22,23,24] . However, the potential and uncertain risks and complication of intravitreal injection (IVI) were noted [24,25,26] . Therefore, we developed the newer, safer and more simple method about deep sub-tenon's injection to treat the CSCR followed by the series of OCT without any complications from the contrast while using fluorescein angiography (FAG) [7] .

2. Material and Methods

Material

From January 2013 to December 2013, consecutive cases with diagnosis of CSCR by OCT, FAG, and ICG (idocyanine angiography). The patients were treated with deep sub-ten injection of Bevacizumab. Patients with the history of preoperative and postoperative anticoagulant therapy, or with a history of blood diseases associated with abnormal coagulation were excluded. After proper disinfection using 5% povidone-iodine and sub-tenon injection of Bevacizumab (0.3 ml) was carried out under topical anesthesia. After treatment, patients were followed at regular intervals. The Snellen best-corrected visual acuity measurement, intraocular pressure, slit-lamp examination and OCT were performed at each follow-up visit.

Case Reports

Case 1 :

A 44-year-old male patient (A management of one foreign company in Taiwan) presented with decreased vision and image distortion in the left eye for 2 weeks. The best-corrected visual acuity (BCVA) was 0.5. The fundus showed elevated and round lesion around the macula of left eye. He had received examinations of FAG and OCT which revealed shallow pigmentary epithelial (RPE) detachment (Fig 1A). The patient was arranged to treat with a deep sub-tenon injection of Avastin (0.3 cc) two times in one month (total two times). Three months later, no inflammatory cells were present in the vitreous and the BCVA had returned to 1.0. The OCT also showed the normal images (Fig 1B, Fig 2B).

Case 2 :

A 17-year-old high-school student presented with sudden diminution of vision in the left eye which he had been experiencing for one month. According to the statement, he likes to play the PC game very much in the smart-phone every days, even three hours in on day. Unfortunately, he developed into blurred vision of left eye (BCVA is only 0.1). In outpatient clinic, the fundus of left eye revealed a sub-retinal fluid beneath macular region (Fig 1A). He received the deep sub-tenon injection of Avastin (0.3 cc) once every month for three months (total three times). We were glad to find out that the left bare vision of this student had returned to 1.0 (BCVA) after five months. At the same time, no apparent complications were found. The RPE detachment disappeared after the 5-month follow-up by OCT. (Fig 2B and 2C). To our knowledge, the student suffering from CSCR in our case is the youngest ill-patient in the world by using the Medline search.

Case 3 :

A 35-year-old male patient who was the sales staff in one pharmaceutical factory in Kaohsiung city (Taiwan). He was aggressive in business and worked hard over 10 hours every day. Suddenly he presented with decreased vision in the right eye over 1 week and his BCVA was limited to only 0.2 in our clinic. After pupil dilated, we found the remarkable CSCR in the posterior pole by OCT (Fig 3A). Then the patient was received with 0.3 cc Avastin by sub-tenon injection three times every month (total 6 times). After regular follow-up for six months, the BCVA had increased to 0.9 with normal anterior and posterior segment findings in series of OCT (Fig 3B).

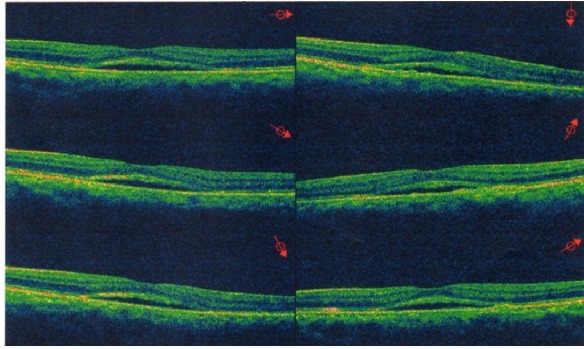


Fig 1A (Initial)

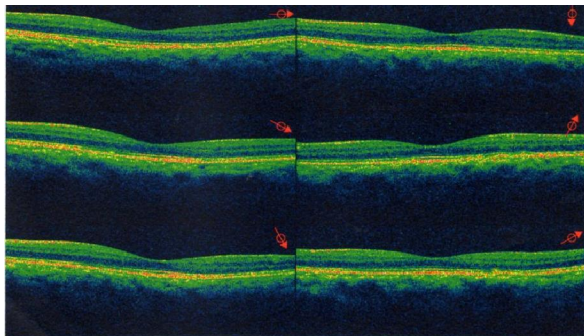


Fig 1B (2 months later)

Fig 1A and B: The OCT showed the disappear of CSCR after deep sub-tenon's injection of Avastin 3CC of left eye after two months (Case 1). (OCT/SLO, OPKO, E-Vision Instrument Company).



Fig 2A : The color fundus showed the protruding and round appearance of macula combined with subretinal fluid retention indicated the CSCR. The best corrected of vision (OS) of the very young male patient aged 17 year-old had dropped into 6/60 within one month (Case 2).

Fig 2 B (Initial)

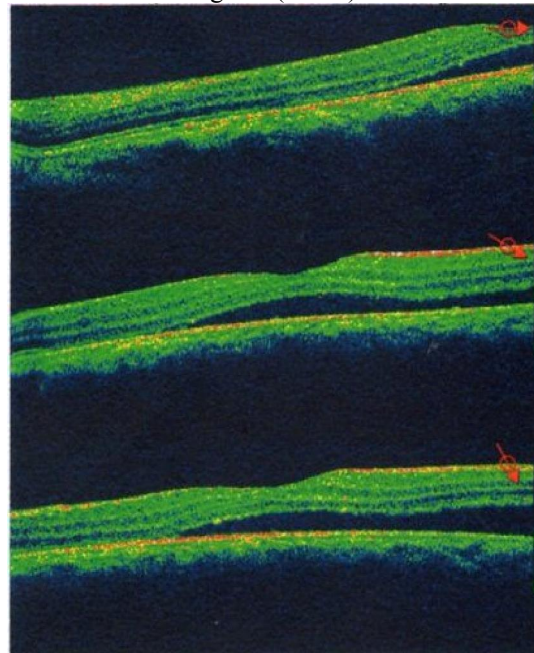


Fig 2 C (after 5 months)

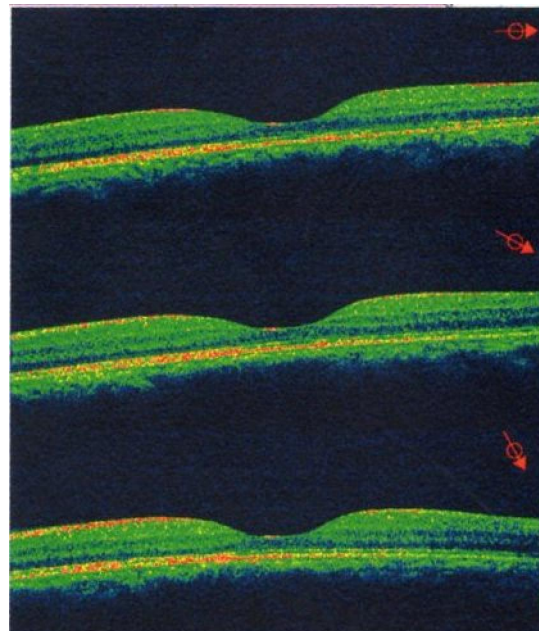


Fig 2 B and C: The OCT revealed the normal fundus after deep sub-tenon's injection of Avastin 3CC (three times) after 5 months (Case 2). (OCT/SLO, OPKO, E-Vision Instrument Company).

Fig 3A (Initial)

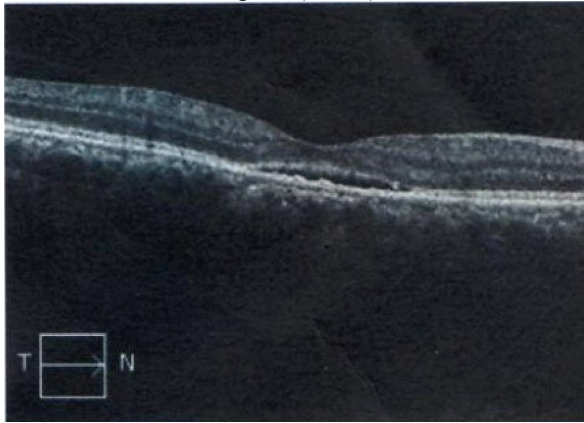


Fig 3B (after 6 months)



Fig 3A and B: The serous retinal detachment disappeared gradually within one month after the deep sub-tenon's injection of Avastin of right eye in the patient with CSCR (OD) (Case 3). (OCT, Staras, Carl Ziess).

3. Discussion

Most of the patients with CSCR may resolve within 4 to 6 months, and a good final acuity of more than 20/40 (bare vision) is observed in 90% of cases [29,30]. Although most of the patients may recover within several months, the inconvenient behavior for example the poor stereopsis may affect the daily work, driving and even eating. Furthermore, color vision and contrast sensitivity are often disturbed [31,32]. What. More, CSCR shows bilateral involvement in 30%, recurrence in 40% and severe visual loss in 5% of chronic course [33,34].

Bevacizumab (Avastin, Genentech Inc. San Francisco, CA), is a full length humanized monoclonal antibody to VEGF; it was approved by the Food and Drug Administration for the treatment of colorectal cancer. It can inhibit both types of VEGF receptors: VEGFR-1 and VEGFR-2. It had been used to treat other ophthalmic diseases such as neovascular ARMD by tackling vascular proliferation. In

the cases of CSCR, VEGF has a role in vascular permeability by changing tight junctions and inducing vascular fenestration [35]. Thus, the new point about using Avastin to handle and short the course of CSCR becomes very popular recently.

Now different series of studies in many researchers such as Kim, Torres-Soriano and Artunay et al. all suggested that the improvement in visual acuity, disappearance of RPE detachment and sub-retinal fluid after anti-VEGF injection [36,37,38]. Some prospective controlled study of patients with chronic CSCR found similar results with any negative effects. Recently, Lim et al. even found that VEGF and interleukin-8 levels in plasma and aqueous humor of patients with CSCR. If treated successfully, the resolution of neuro-sensory detachment may improve after Avastin injection [39]. Therefore, the correct and rapid use of the anti-VEGF agents should be taken into consideration in solving the problems of CSCR.

Over the last decades, the use of IVI has gained increasing acceptance in the therapeutic management of many intraocular diseases, affecting the posterior segment. For example, we can use the IVI of antiviral agents in treating the cytomegalovirus (CMV) retinitis. In addition, IVI of various gases (SF₆ or C₃F₈) has been used for the management of retinal detachment in the setting of pneumatic retinopexy. Recently IVI of triamcinolone acetonide (Kenolog) is used to treat many ocular disorders including macular edema, retinal edema and retinal neo-vascularization [40].

The potential advantages of IVI became more widely appreciated and the number of possible applications has been grown. With over 15,000 annual IVI worldwide, Bevacizumab is rapidly becoming one of the popular methods in the treatment of many diseases. However, many trouble questions have arisen regarding risks associated with the route of administration. Several potential complications of IVI can be vision-threatening and even life-threatening. Surprisingly, systemic adverse events were reported. Anti-VEGF agents gain access to the systemic circulation following IVI. Systemic blockade can give rise to various complications. These may include acute elevation of systemic blood pressure, epistaxis, hemoptysis, proteinuria, delayed wound healing after surgery, and impaired reproductive function [41,42]. Other severe problems included the cerebrovascular accidents (CVA), myocardial infarctions (MI), iliac artery aneurysms, toe amputations and even deaths [43]. Besides, 5% of all patients using systemic bevacizumab in combination with chemotherapy may have an increased risk of developing the serious or fatal thromboembolic events. Ocular complications

including increased intraocular pressure, cataract formation, bacterial endophthalmitis, tractional retinal detachment, uveitis, rhegmatogenous retinal detachment and vitreous hemorrhage were usually found in many reports [44]. Some of these problems may be solved by lowering IOP agents, topical steroids and even further surgery. However, the possibilities of vision loss may be threatening to the ill-patients. For example, bacterial endophthalmitis is unexpected and dreaded complication of any IVI. The rate varies from 0.04% to 0.33%. Sterile technique and antisepsis with instillation of topical povidone iodine 5% into the conjunctival fornix prior to IVI may reduce the risk of endophthalmitis[45]. However, risk assessment of IVI is complex, and some studies were suggested the ophthalmologists to use the method of IVI carefully. Moreover, the occurrence of complications directly related to the toxicity of administration compounds confounds of complications related to IVI itself [46] .

Another issue that has been addressed is the legal problem resulting from complications occurring with off-label therapy. Bevacizumab is not legally approved for intraocular use in Taiwan. Intraocular inflammation has been reported with IVI of bevacizumab. The possibility of myocardial infarction, stroke and even mortality may impact the relationship between patients and ophthalmologists. The doctors may be bothered by annoying medical disputes. In our reports, the use of sub-tenon's injection was the safer approach. No local or systemic complications were found. The pharmacokinetic characteristics of compounds of sub-tenon's injection still remained unknown and deserved further study. However, the technique may be another alternative.

There are exactly various imaging modalities that would be used to make diagnosis of CSCR. Large and elevated dome-shape over the macula should be examined by experienced ophthalmologists under indirect ophthalmoscope. However, the incidence was relatively low. The early technique was FAG which has been the most widely used imaging techniques thirty years ago. The most important angiographic feature is an expanding point of fluorescein leakage (so called pinpoint leakage) under the serous detachment of the neuro-sensory retina without any sub-retinal NV [35,47] . The FAG can correctly showed 95% CSCR, and the most common sites of leakage are the super-nasal quadrant of the posterior pole. In some cases of chronic CSCS, FAG may be the useful method. However, contrast medium should be necessarily injected to the vein for further evaluation, and some patients should suffer from allergic reactions such as yellow urine, flushing of the face, dermatitis, shortness of breath, asthma, and even shock. Thus, some of the patients were hesitated to

decide to receive this invasive procedure. In the series of study of Matsuura et al., FAG was performed in 1,499 of the 1,500 cases. Adverse reactions such as nausea, cough, cold sweat, urticaria, and shock were noted in 85 cases (5.7%). Typical drug-induced shock occurred in one case (0.07%). Hence, high probability of anaphylactoid shock due to FAG, and hence the examinations were appealed for cancellation in Japan [48] . In some studies in Ceze, the same suggestion were also emphasized about the improvement of nature history of acute CSCR and help to repair the tight junctions recently [49] .

Twenty years ago, ICG were widely used to describe abnormalities in choroidal circulation in which the primary pathology in CSCR occurs. Filling delayed have been reported as occurring from 63 to 100% of CSCR in choroidal hyper-permeability [50,51] . It may easily reveal the area of RPE occurring in choroidal capillary or venous congestion. The cases of CSCR had been observed from 37 to 96 % patients by the use of ICG [52] . Although adverse reactions to ICG are known to occur, the dye has been used for more than 30 years in tests of cardiac and hepatic function, with a high level of safety compared with FAG. Recently, Hope-Ross M et al. also reported that there was 0.15% mild, 0.2% moderate, and 0.05% severe adverse reactions in patients with CSCR who received the examination of ICG [53] .

Although the gold standard for CSCR diagnosis is FAG which displays sub-retinal fluid accumulation, RPE detachment and dye leakage from the choroid into the sub-retinal fluid, now it is instead of OCT, a non-invasive diagnostic technique, that uses reflection of light off the retinal layers to create a false-color tomographic image of the retina and RPE [5] . Recently three-dimensional OCT and the en face OCT ophthalmoscope have been to given even more detailed imaging [54] . Van Velthoven et al. ever assessed 38 eyes with CSCR with OCT and easily followed the patients with both active and in-active CSCR that can be present in and outside areas of serous detachment. There were diffuse RPE involvement combined with multiple small pigment epithelial detachment in the macula and vascular arcades of a third of the eyes. Imamura et al. demonstrated that significantly increased choroidal thickness in CSCR patients and the mean thickness were found to be 505 μm [55] . Montero and Ruiz-Moreno [56] also exactly found that 90% of 39 eyes with CSCR using OCT [57] . Now the special characteristics of safety without injection any contrast medium make the OCT become very famous in ophthalmic clinics and researches now. Even Hiram

et al. had compared the more exact diagnostic rate in OCT (88%) than FA (69%) [59] . Wang et al. also had the same comments [60] . Thus, we suggested that the doctors can use the series of changes of posterior pole by OCT to evaluate the outcome of CSCR after sub-tenon injection.

4. Conclusion

Deep sub-tenon injection of bevacizumab was effective in the treatment of CSCR without safety concerns. It can induce the effectively repair of tight junction of RPE and rapid regression of sub-retinal fluid. This method was shown to be safer than IVI. Besides, the optic beam in OCT can make the cross-section through all 10 layers of the retina, the histological examination, and show edema of retina clearly. Therefore, it is a non-invasive method to make diagnosis of the prognosis of CSCR after various treatments.

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