Graefes Arch Clin Exp Ophthalmol (2008) 246:1235–1239
DOI 10.1007/s00417-008-0856-x

RETINAL DISORDERS

A pilot study of intravitreal bevacizumab for the treatment of central serous chorioretinopathy (Case reports)

Mitzy E. Torres-Soriano · Gerardo García-Aguirre · Verónica Kon-Jara · Orlando Ustariz-Gonzáles · Maura Abraham-Marín · Michael D. Ober · Hugo Quiroz-Mercado

Received: 2 October 2007 / Revised: 3 April 2008 / Accepted: 28 April 2008 / Published online: 4 June 2008

Abstract
Background We report the use of intravitreal bevacizumab as a new option in the treatment of central serous chorioretinopathy (CSC).
Methods Five eyes with retinal pigment epithelium (RPE) leaks secondary to CSC received intravitreal bevacizumab (2.5 mg/0.1 cc), and underwent best corrected visual acuity, fluorescein angiography and optical coherent tomography before, 1, 3 and 6 months after treatment.
Results All patients showed improvement in visual acuity, fluorescein angiographic leakage, and reduced or resolved neurosensory detachment following treatment.
Conclusions Intravitreal injection of bevacizumab was associated with visual improvement and reduced neurosensory detachment without adverse events in patients with CSC. Although these results are promising, further investigations would be helpful to understand this therapy for patients with CSC.

Keywords Central serous chorioretinopathy · Intravitreal bevacizumab · Retinal pigment epithelium detachment

M. E. Torres-Soriano (✉) · G. García-Aguirre · V. Kon-Jara · O. Ustariz-Gonzáles · M. Abraham-Marín · H. Quiroz-Mercado
Retina Service, Asociacion Para Evitar la Ceguera,
Hospital Dr. Luis Sánchez Bulnes,
Vicente García Torres 46, San Lucas Coyoacan,
04030 Coyoacan, México City, México
e-mail: mitzytorres@yahoo.com

M. D. Ober
LuEsther T. Mertz Retinal Research Center, Manhattan Eye,
Ear and Throat Hospital,
New York, NY, USA

M. D. Ober
Vitreous-Retina Macula Consultants of New York,
New York, NY, USA

Introduction

Central serous chorioretinopathy (CSC) was first described by Von Graefe in 1866 and termed "recurrent central retinitis" [15]. It is a well-characterized disorder leading to serous neurosensory elevation of the retina. The acute form of the disease is associated with focal leakage at the level of the retinal pigment epithelium (RPE)—demonstrated with fluorescein angiography (FA), and hyperpermeability of the choroid—demonstrated with indocyanine green angiography [8]. The disorder is self-limited in the majority of patients, who usually retain excellent vision. Those who do not resolve spontaneously can develop pigment epithelial and photoreceptor damage, resulting in permanent visual impairment.

The pathophysiology of CSC remains poorly understood; however, the cascade of events leading to neurosensory detachment includes, and may in fact begin with the changes in choroidal permeability. Bevacizumab (Avastin, Genetech), an antibody to vascular endothelial growth factor (VEGF), has known antipermeability properties and therefore may theoretically reverse the changes seen in CSC. This article describes the use of intravitreal bevacizumab as a new option in the treatment of CSC.

Materials and methods

Patients with a diagnosis of CSC with history of decreased visual acuity >3 months, recurrent episodes of CSC or acute cases with excessive discomfort about visual acuity were included. All patients had idiopathic neurosensory retinal elevation demonstrated by optical coherent tomography (OCT), and presence of focal leaks at the level of the RPE on fluorescein angiography (FA). Patients underwent

detailed informed consent, with special attention paid to the known side effects of systemic bevacizumab administration, and were excluded from treatment if they had a significant cardiovascular or thromboembolic history or were pregnant. All patients received intravitreal injection of bevacizumab (2.5 mg in 0.1 ml) under standard protocol conditions. Each patient underwent best corrected visual acuity measurements (Snellen or Early Treatment Diabetic Retinopathy Study charts (ETDRS), slit-lamp examination and dilated retinal fundoscopy, as well as OCT and FA at baseline, 1, 3 and six months after treatment.

Case reports

Case 1

A 30-year-old male dental surgeon presented with complaints of decreased visual acuity in the left eye for 2 months and excessive discomfort with his visual acuity that interfered with his daily activities. ETDRS visual acuity measured 20/40. Fluorescein angiography revealed a focal RPE leak just temporal to the fovea with surrounding neurosensory detachment, confirmed by OCT. Moreover, OCT revealed RPE and neurosensory detachment adjacent to and including the fovea. After discussing treatment options, the patient was injected intravitreally with 2.5 mg of bevacizumab in the left eye. Visual acuity improved to 20/20 at 2 months after treatment, with concurrent resolution of symptoms, fluorescein leakage, as well as RPE and neurosensory detachment. At 6-month follow-up the visual acuity, OCT and FA were unchanged.

Case 2

A 61-year-old male professional driver with a history of CSC complained of worsened vision and central scotoma in the left eye for 4 months. Visual acuity at the time of presentation measured 20/80. Fluorescein angiography revealed a focal RPE leak just superior to the fovea with surrounding neurosensory detachment confirmed by OCT. Visual acuity improved to 20/25 1 month following intravitreal bevacizumab, with reduction of fluorescein angiographic leakage, and resolution of neurosensory detachment on OCT. At 3 and 6 months after treatment the visual acuity improved to 20/20; resolution of fluorescein leakage but persistent atrophy of RPE was observed.

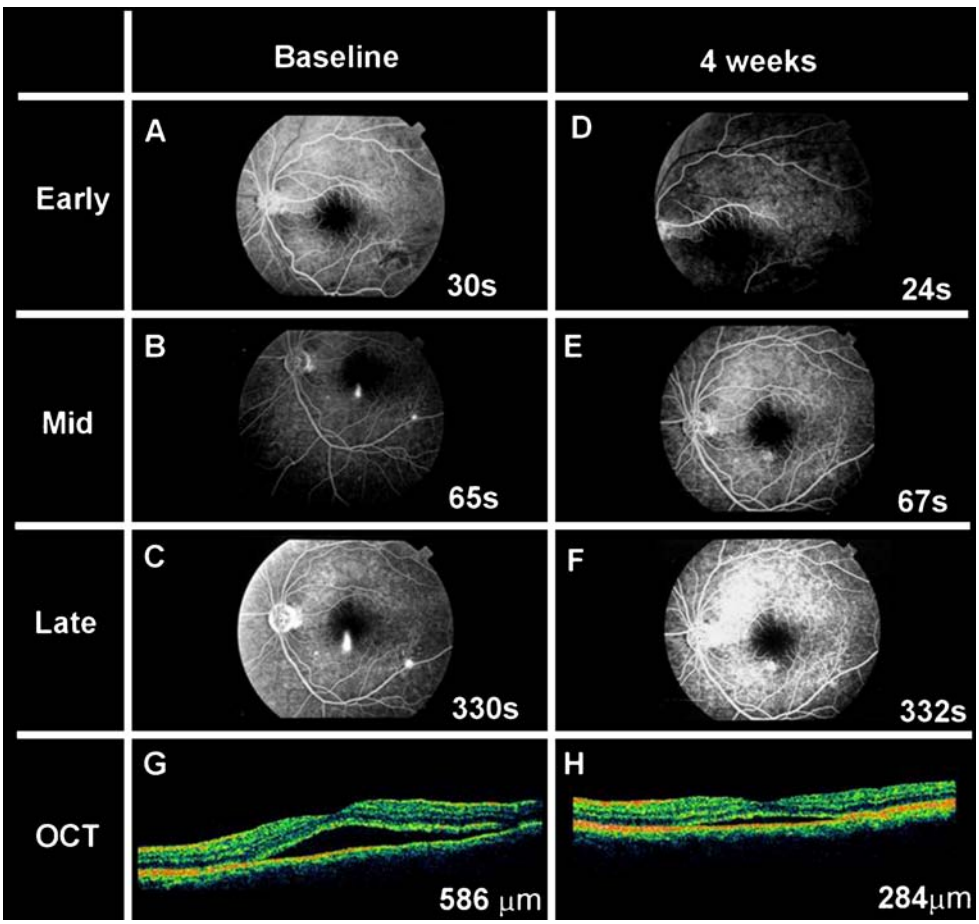

Fig. 1 **a**,**b**,**c** Early-phase fluorescein angiogram (FA) didn't show any point of leakage. Mid and late phases showed two areas of focal hyperfluorescence with characteristic smoke-stack configuration. **d**,**e**,**f** FA revealed mottled hyperfluorescence because of atrophic changes of RPE during earlier and later phases. **g** Vertical-line optical coherence tomography (OCT) before treatment confirmed the presence of a serous neurosensory detachment under the fovea and 586 μm of thickness. **h** Vertical line OCT demonstrated a partial resolution of neurosensory detachment after treatment

Case 3

A 36-year-old male with a history of recurrent episodic CSC and visual acuity of 20/40 in the left eye presented with 2 months of new symptoms including decreased vision and metamorphopsia. Ophthalmologic examination revealed neurosensory elevation of the central macula, and FA showed a focal RPE leak inferior to the fovea. Optical coherence tomography revealed an RPE detachment that involved the fovea. Treatment with 2.5 mg of intravitreal bevacizumab was given. Visual acuity improved to 20/25 1 month after treatment, with improvement of both fluorescein leakage and neurosensory detachment. No changes were observed at 6-month follow-up. (Fig. 1).

Case 4

A 37-year-old male presented with a 12-month history of decreased visual acuity in his left eye. At the time of presentation, visual acuity was 20/50. Fluorescein angiography revealed a focal RPE leak near to the fovea with surrounding neurosensory detachment confirmed by OCT, and was treated with 2.5 mg of intravitreal bevacizumab. His visual acuity improved to 20/30 1 month after treatment, with decreased neurosensory detachment demonstrated by OCT and improvement in symptoms. However, angiographic leakage persisted. At 3- and 6-month follow-up no subretinal fluid was observed by OCT, and visual acuity improved to 20/20. (Fig. 2).

Case 5

A 20-year-old female with a history of recurrent episodic CSC and visual acuity of 20/40 in the left eye presented with 2 months of decreased vision and metamorphopsia. Examination revealed neurosensory elevation of the central macula, and FA showed a focal RPE leak that involved the fovea. Optical coherence tomography revealed an RPE and neurosensory detachment through the fovea. Visual acuity improved to 20/20 1 month after intravitreal bevacizumab, with improvement of both fluorescein leakage and neurosensory detachment. Three and 6 months after treatment, no neurosensorial retinal detachment or fluorescein leakage were observed. (Fig. 3).

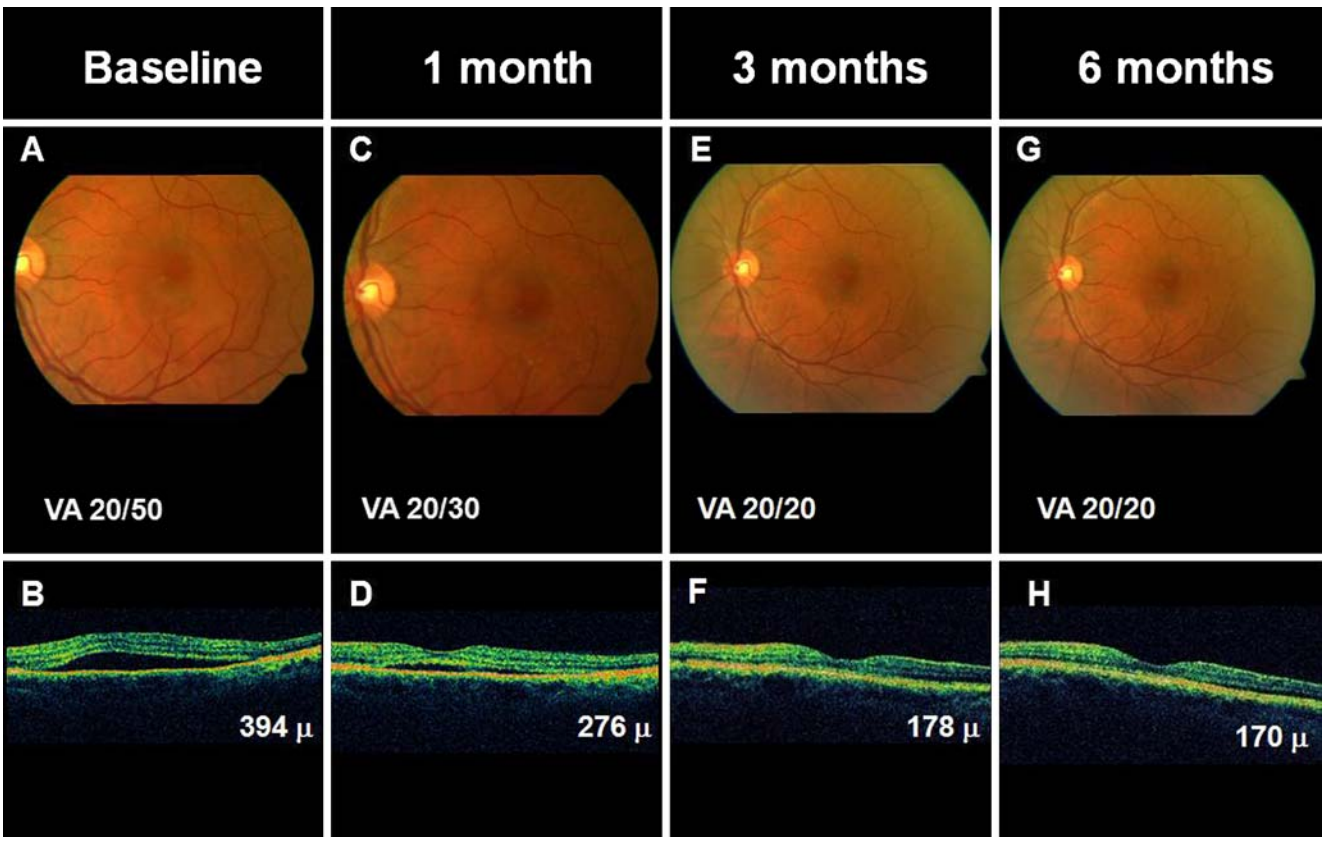

Fig. 2 **a**,**b** Fundus image and vertical line OCT before treatment. Visual acuity was 20/50, and OCT revealed presence of a serous neurosensory detachment under the fovea and 394 µm of thickness. **c**, **d** Some changes of RPE were observed at fundus image, visual acuity improved to 20/30 and vertical line OCT demonstrated a partial resolution of neurosensory detachment after treatment. **e**,**f**,**g**,**h**. Visual acuity improved to 20/20 and OCT showed complete resolution at 6-month follow-up

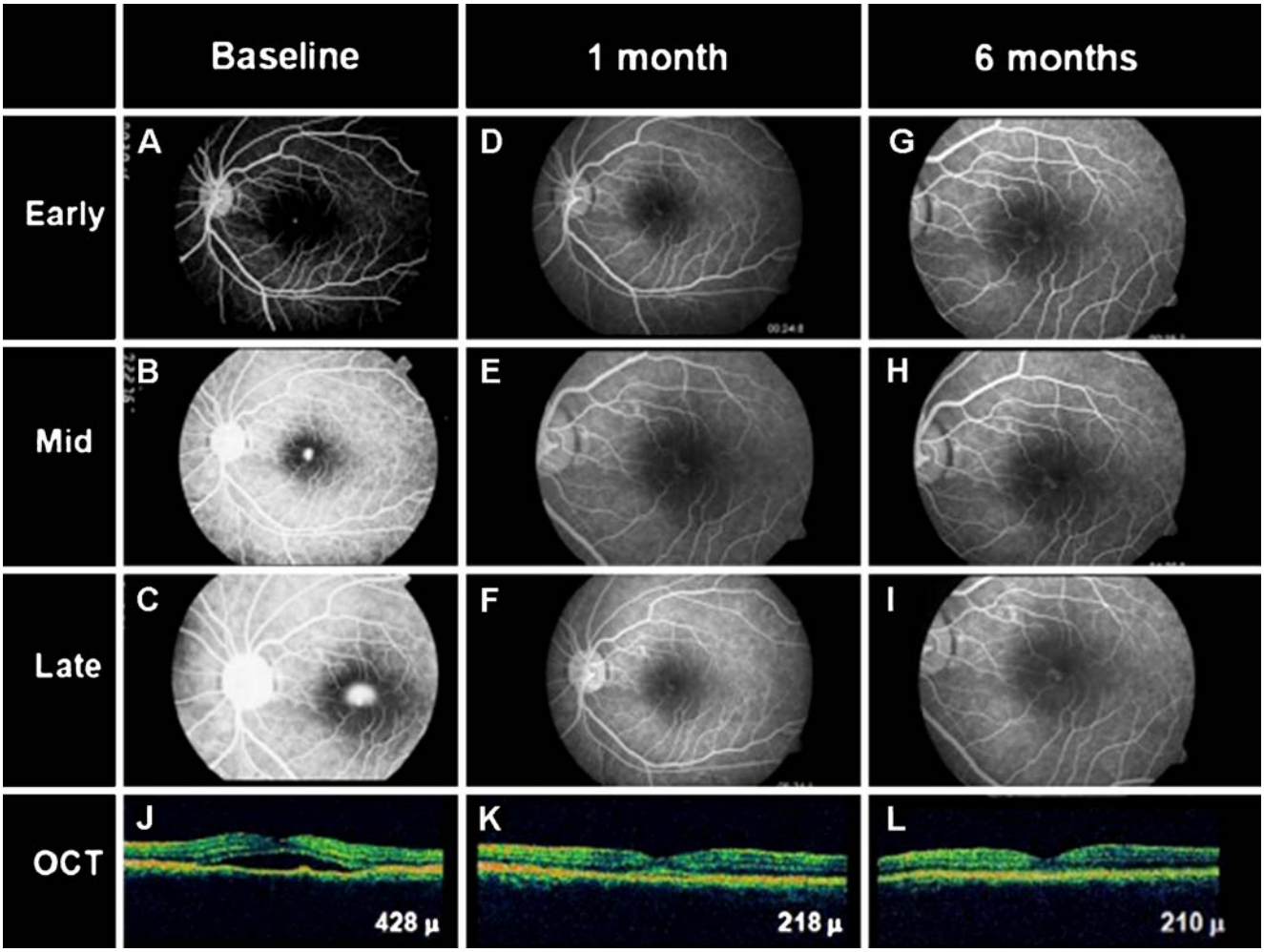

Fig. 3 **a**,**b**,**c** FA before the treatment demonstrated in early phase a pinpoint of leakage. Mid and late phases showed increase of leakage. **d**,**e**,**f**,**g**,**h**,**i** Early, mid and late phases of FA after treatment revealed mild hyperfluorescence in to the fovea, without leakage. **j**,**k**,**l** Vertical line OCT before treatment demonstrated the presence of a serous neurosensory detachment under the fovea and 428 µm of thickness. One month after treatment, OCT showed minimal subretinal fluid, and showed resolution at 6-month follow-up

Discussion

Various medical treatments have also been attempted for this disorder, including acetazolamide [12], beta-blockers [3], vitamins, non-steroidal anti-inflammatory medications, all without decisive benefit.

The literature has mixed recommendations on the use of thermal laser [4] for CSC, with some authors reporting that laser photocoagulation shortens the duration of disease and reduces the recurrence rate, while others maintain that it does not improve final vision, recurrence rates, or progression to chronic CSC. Furthermore, laser photocoagulation is associated with permanent scotomata which may enlarge over time with RPE scar expansion, as well as the possible development of CNV.

Most recently, several case series have reported the use of indocyanine green guided photodynamic therapy to treat chronic CSC [2]. Ober and associates [11] reported the successful treatment of focal RPE leaks in CSC by PDT in a small pilot series which did show resolution and visual improvement. Cardillo Piccolino et al. performed ICG-guided PDT in 16 eyes with chronic CSC and treatment resulted in complete resolution of serous retinal detachment 1 month after treatment in 75% of eyes. At 3 months after PDT, 69% of eyes had visual improvement of 1 or more lines. In this study, 31% of eyes developed secondary RPE changes at the site of PDT, which were thought to be due to hypoxic damage caused by choriocapillaris occlusion [5]. However, photodynamic therapy is expensive and cases of CNV have been reported following treatment for CSC [6, 7].

The pathophysiology of CSC remains controversial, despite over 145 years having passed since its discovery. Recent OCT and autofluorescence data has shown that small tears in the RPE are the cause of focal fluorescein leaks viewed as the source of neurosensory detachment [10], but clues to the initial stages of the disease have

proven more elusive. The advent of indocyanine green (ICG) angiography presented evidence of choroidal involvement in the disease. ICG findings include zones of hyperpermeability that manifest as hyperfluorescence on mid frames of the examination. Areas of RPE detachment and focal fluorescein leakage are always found with these hyperpermeable areas; however, zones of hyperpermeability are also located in isolated areas which may be otherwise asymptomatic. In fact, these ICG abnormalities may be the only signs of disease in otherwise unaffected eyes. For these reasons, it is likely that choroidal hyperpermeability is an early event in the development of symptomatic CSC where, under the appropriate circumstances, it may lead progressively to RPE detachment followed by neurosensory detachments.

Bevacizumab is a full-length antibody that binds all isoforms of VEGF. Intraviteal bevacizumab has not been tested in a randomized, controlled fashion; however, a growing number of reports in the literature support its safety and efficacy in many disorders [1, 14]. We do not know the mechanism by which intravitreal bevacizumab works in CSC, but we believe it may be related to its ability to affect vascular permeability. The direct role of VEGF in CSC is also unknown, and the authors do not know of any study which has reported VEGF levels in patients with CSC.

VEGF was formerly known as "vascular permeability factor", and has profound effects on vascular permeability. Theoretically, reduced levels of VEGF may ameliorate the choroidal hyperpermeability in CSC, although ICG angiograms would be necessary to evaluate this, and they were not performed in these cases. There is controversy over the ability of bevacizumab to penetrate the retina and reach the choroid; however, recent reports suggest that it does indeed do so [9, 13], which supports the possibility that an intravitreal injection of bevacizumab may be biologically active in areas of choroidal hyperpermeability.

There are many sources of error in this pilot study, including the small number of patients, short follow-up and the fact that we included various forms of CSC. There is also no data available to support or refute the proposed mechanism of action. Indeed, it is possible that all five cases underwent spontaneous improvement or resolution that was simply coincident with their treatments. Nevertheless, the improvement in RPE and neurosensory detachments, as well as visual acuity but not necessarily disease resolution, suggests that intravitreal bevacizumab may be efficacious in the treatment of CSC. In general, CSC is associated with a favorable prognosis and we can not make specific treatment recommendations based on this small, uncontrolled case series. However, further investigations into both the possible role of VEGF in the pathogenesis of CSC and treatment of CSC with anti-VEGF agents are warranted.

References

1. Avery RL, Pieramici DJ, Rabena MD, Castellarin AA, Nasir MA, Giust MJ (2006) Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. Ophthalmology 113:363–372
2. Battaglia Parodi M, Da Pozzo S, Ravalico G (2003) Photodynamic therapy in chronic central serous chorioretinopathy. Retina 23:235–237
3. Bujarborua D (2005) CSR: Idiopathic central serous chorioretinopathy. Jaypee Brothers, New Delhi
4. Burumcek E, Mudun A, Karacorlu S, Arslan MO (1997) Laser photocoagulation for persistent central serous retinopathy: results of long-term follow-up. Ophthalmology 104:616–622
5. Cardillo Piccolino F, Eandi CM, Ventre L et al (2003) Photodynamic therapy for chronic central serous chorioretinopathy. Retina 23:752–763
6. Chan WM, Lam DS, Lai TY et al (2003) Choroidal vascular remodeling in central serous chorioretinopathy after indocyanine green guided photodynamic therapy with verteporfin: a novel treatment at the primary disease level. Br J Ophthalmol 87:1453–1458
7. Colucciello M (2006) Choroidal neovascularization complication photodynamic therapy for central serous retinopathy. Retina 26:239–242
8. Gass JD (1967) Pathogenesis of disciform detachment of the neuroepithelium. Am J Ophthalmol 63(Suppl):1–139
9. Heiduschka P, Fietz H, Hofmeister S, Schultheiss S, Mack AF, Peters S, Ziemssen F, Niggemann B, Julien S, Bartz-Schmidt KU, Schraermeyer U (2007) Tübingen bevacizumab study group. Penetration of bevacizumab through the retina after intravitreal injection in the monkey. Invest Ophthalmol Vis Sci 48:2814–2823
10. Ober MD, Eandi CM, Jampol LM, Fine HF, Yannuzzi LA (2007) Focal retinal pigment epithelium breaks in central serous chorioretinopathy. Retinal Cases and Brief Reports 1(4):271–274
11. Ober MD, Yannuzzi LA, Do DV et al (2005) Photodynamic therapy for focal retinal pigment epithelial leaks secondary to central serous chorioretinopathy. Ophthalmology 112:2088–2094
12. Pikkel J, Beiran I, Ophir A, Miller B (2002) Acetazolamide for central serous retinopathy. Ophthalmology 109:1723–1725
13. Shahar J, Avery RL, Heilweil G, Barak A, Zemel E, Lewis GP, Johnson PT, Fisher SK, Perlman I, Loewenstein A (2006) Electrophysiologic and retinal penetration studies following intravitreal injection of bevacizumab (Avastin). Retina 26:262–269
14. Spaide RF, Laud K, Fine HF et al (2006) Intravitreal bevacizumab treatment of choroidal neovascularization secondary to age-related macular degeneration. Retina 26:383–390
15. Von Graefe A (1866) Ueber centrale recidivierende Retinitis. Graefes Arch Clin Exp Ophthalmol 12:211–215