European Journal of Ophthalmology / Vol. 17 no. 4, 2007 / pp. 620-626

Intravitreal bevacizumab (Avastin) as primary treatment for myopic choroidal neovascularization

S. MANDAL, P. VENKATESH, R. SAMPANGI, S. GARG

Dr. Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi - India

PURPOSE. *To evaluate the short-term efficacy and safety of intravitreal bevacizumab in myopic choroidal neovascularization (mCNV).*

METHODS. *In this noncomparative, consecutive, interventional case series, 12 eyes of 11 patients with mCNV without any previous treatment were included. Patients received intravitreal bevacizumab (1.25 mg/0.05 mL) at baseline and at 4 weeks interval, if optical coherence tomography (OCT) showed presence of intraretinal edema, subretinal fluid, and/or pigment epithelial detachment. Patients were followed up for a minimum of 6 months and changes in best-corrected visual acuity, central macular thickness (CMT) on OCT, angiographic characteristics, and complications were assessed.*

RESULTS. *The mean refractive error was -11.25 diopters. At 6 months the mean best-corrected visual acuity (BCVA) improved from 20/235 (median 20/235) to 20/71 (median 20/80) (p=0.01). The mean CMT was reduced from 403 µm (median 365 µm) to 229 µm (median 239 µm) (p=0.002). At final visit 9 eyes (75%) had an improvement of BCVA of three lines or more, and only 1 eye (8%) lost two lines. No significant ocular or untoward systemic side effects were observed.*

CONCLUSIONS. *In this small series short-term results suggest that intravitreal bevacizumab (1.25 mg/0.05 mL) is safe, effective, and well tolerated in patients with choroidal neovascularization due to high myopia. Further evaluation in large series with longer follow-up is needed to confirm long-term efficacy and safety in such cases. (Eur J Ophthalmol 2007; 17: 620-6)*

KEY WORDS. *Bevacizumab, Myopic choroidal neovascularization, Optical coherence tomography*

Accepted: March 12, 2007

INTRODUCTION

Choroidal neovascularization (CNV) is a significant cause of central vision loss in young and middle-aged patients with high myopia.

Although various therapies like thermal laser photocoagulation (1, 2), photodynamic therapy (PDT) (3-5), and surgical removal of myopic CNV (mCNV) (6) have been tried, none of them has been proven to be effective in the treatment of mCNV.

PDT with verteporfin has been the standard and only approved treatment for subfoveal CNV due to pathologic myopia (3). In cases with poor response to PDT, management options are very limited. Also, long-term results of PDT are not significantly different from placebo (4).

The introduction of anti-VEGF agents has resulted in a new treatment option for CNV management. Off-label use of bevacizumab has become a leader among the anti-VEGF agents in the management of CNV because of reported encouraging results and low cost. The purpose of the present study was to determine the efficacy and safety of intravitreal injection of bevacizumab as primary treatment modality in the management of mCNV.

1120-6721/620-06$15.00/0

PATIENTS AND METHODS

The study was a noncomparative, consecutive, interventional study to evaluate the short-term efficacy and safety of intravitreal bevacizumab in patients with CNV due to high myopia.

Patient selection

Twelve consecutive cases of mCNV were enrolled in this study.
Informed consent was obtained from each eligible patient after explaining the potential risks and benefits of intravitreal bevacizumab including its off-label use. Hypertension and history of thromboembolic event were ruled out before intravitreal injections. Only patients with a minimum follow-up of 6 months were included in this study.
Before treatment, full ophthalmologic examination was done, including retinal periphery examination with indirect ophthalmoscopy to rule out any breaks. Best-corrected visual acuity (BCVA) was recorded with standard Snellen chart. Color fundus photography, fluorescein angiography, and fast macular scan and line scan by optical coherence tomography (OCT) (Stratus OCT, Carl Zeiss Meditec, Dublin, CA) were done before treatment.

Intravitreal bevacizumab injection and follow-up assessment

A 0.2 mL aliquot of commercially available bevacizumab (25 mg/mL) (Avastin, Genentech, San Francisco, CA) was prepared for each patient in the ocular pharmacology department of our center. The aliquots were stored at 4 to 8 °C. One aliquot was used for single injection. After preparing the eye with 5% povidone iodine, 1.25 mg (0.05 mL) of bevacizumab was injected intravitreally via the pars plana using 26-gauge needle. After injection, intraocular pressure was checked and one drop of gatifloxacin eyedrop was instilled. The eye was bandaged for 3 to 4 hours and patients were instructed to instill topical gatifloxacin eyedrops four times a day for the next 4 days. Patients were called on the next day to ask about any complication and then at 4 weeks interval. At each visit full ophthalmologic examination including BCVA, fundus photography, and OCT was done. Blood pressure was also monitored. Intravitreal injection was repeated at 4 weeks interval if OCT showed persistent intraretinal edema, subretinal fluid (SRF), and/or pigment epithelial detachment (PED). Fluorescein angiography was repeated at 12 weeks interval. Retinal thickness was assessed by OCT using fast macular scan.

Statistical analysis

Snellen visual acuity was converted to logarithm of minimum angle of resolution (logMAR) equivalent. Data were recorded on an Excel spreadsheet. All the entries were checked for any possible keyboard error.
For data analysis, statistical software STATA version 9.0 (College Station, TX) was used. Data were expressed as mean (±SD) and median (range). Visual and OCT parameters were compared at baseline and 1 month, 3 months, 6 months, and last visit. Wilcoxon signed ranks test was used for comparison of data as they were not normally distributed. In this study $p<0.05$ was considered statistically significant.

RESULTS

Twelve eyes of 11 patients with mCNV were included in this study. The average age of the patients was 46.5 years with a range of 21 to 67 years. There were four male and seven female patients. The mean refractive error was –11.25±3.2 diopters, ranging from –7 to –16 diopters.
The Snellen BCVA at baseline ranged from counting fingers at 2 feet to 20/80, with a median of 20/235. The mean ± standard deviation (SD) logMAR BCVA before treatment was 1.30±0.54 (20/400 in Snellen equivalent). Mean baseline CMT on optical coherence tomography was 403.67±110.84 µm (median=365 µm). On fluorescein angiography all cases demonstrated classic CNV, of which nine were subfoveal, two were juxtafoveal, and one was extrafoveal (within the papillomacular bundle). The patients were followed up for a mean period of 7.08±1.7 months (range 6 to 12 months).

Visual outcomes (Tab. I)

The Snellen BCVA at 4 weeks ranged from counting fingers at 2 feet to 20/30 with median of 20/100. The mean logMAR BCVA was 0.87±0.55 and the improvement from baseline was significant (p= 0.006).
At 3 months and 6 months the mean logMAR BCVA was 0.80±0.59 (median 20/80) (p=0.005) and 0.78±0.60 (median 20/80) (p=0.005), respectively. Maximum improvement

in BCVA occurred at 4 weeks after one injection. However, further improvement was observed in subsequent follow-up also.

Eight eyes (67%) had final BCVA of 20/80 or more. One eye had baseline BCVA of finger counting at 2 feet and did not improve after injection. Two other eyes had little improvement of BCVA from finger counting at 2 feet to 20/800. One eye lost two lines of BCVA at final visit. BCVA improvement of three lines or more was seen in nine eyes. The mean improvement in BCVA was +4.3 lines at 4 weeks and +5.1 lines (range –2 to +17) at 6 months.

Optical coherence tomographic outcomes (Tab. II)

At 4 weeks follow-up, 6 of 12 eyes demonstrated marked decrease in retinal thickness and complete resolution of SRF and/or PED. At 3 months after injection, five more of the remaining six eyes had resolution of retinal edema, SRF, and/or PED. At 6 months, no eye had retinal edema, SRF, or PED.

The central macular thickness at 4 weeks, 3 months, and 6 months was 243.5±69.78 µm (median=245.5 µm), 239.25±58.31 µm (median=244.5 µm), and 229.41±64.14 µm (median=239 µm), respectively. The decrease in CMT from baseline was significant at each follow-up and maximum reduction of CMT was observed at 4 weeks after first injection. At 6 months average reduction was 174.25 µm (p=0.002).

Fundus fluorescein angiography (FFA)

FFA was done at baseline, 3 months, and 6 months postinjection. At baseline all eyes showed classic CNV. Nine eyes had subfoveal, two eyes juxtafoveal, and one eye extrafoveal CNV. At 6 months postinjection, all eyes showed diminution of leakage, with seven eyes showing no leakage and only staining of CNV scar. Clinical course of mCNV is shown in Figures 1 and 2.

Repeat intravitreal injections

OCT findings were used to decide retreatment. Intravitreal bevacizumab injection was repeated after 4 weeks if OCT showed intraretinal edema, presence of SRF, and/or RPED. The mean number of injections per eye was 1.58 (range 1 to 3). Six eyes required single injection, five eyes required two injections, and one eye required three injections for resolution as per OCT findings.

Safety and complications

The injection was well tolerated by all patients. One patient complained of black floaters on the day of injection and another patient developed mild iridocyclitis. None of the treated patients developed vitreous hemorrhage, retinal tear, retinal detachment, endophthalmitis, cataract, or

TABLE I - SNELLEN BEST-CORRECTED VISUAL ACUITY (BCVA) AT BASELINE AND EACH FOLLOW-UP

Visual parameters	Preinjection	4 wk	3 mo	6 mo
Snellen BCVA, mean ± SD	0.08±0.07	0.23±0.19	0.27±0.20	0.28±0.21
Snellen BCVA, median (range)	0.1 (0.01–0.25)	0.2 (0.01–0.67)	0.25 (0.01–0.67)	0.25 (0.01–0.67)
p* Value (compared to baseline)		0.01	0.01	0.01

*Wilcoxon signed rank test

TABLE II - OPTICAL COHERENCE TOMOGRAPHIC (OCT) PARAMETERS AT BASELINE AND EACH FOLLOW-UP

OCT parameter	Preinjection, mean ± SD; median (range)	4 wk, mean ± SD; median (range); p value*	3 mo, mean ± SD; median (range); p value*	6 mo, mean ± SD; median (range); p value*
Central macular thickness	403.66±110.84; 365 (294–667)	243.50±69.78; 245.5 (97–313); 0.002	239.25±58.31; 244.5 (101–314); 0.002	229.41±64.14; 239.5 (108–321); 0.002

*Compared to baseline, Wilcoxon signed ranks test

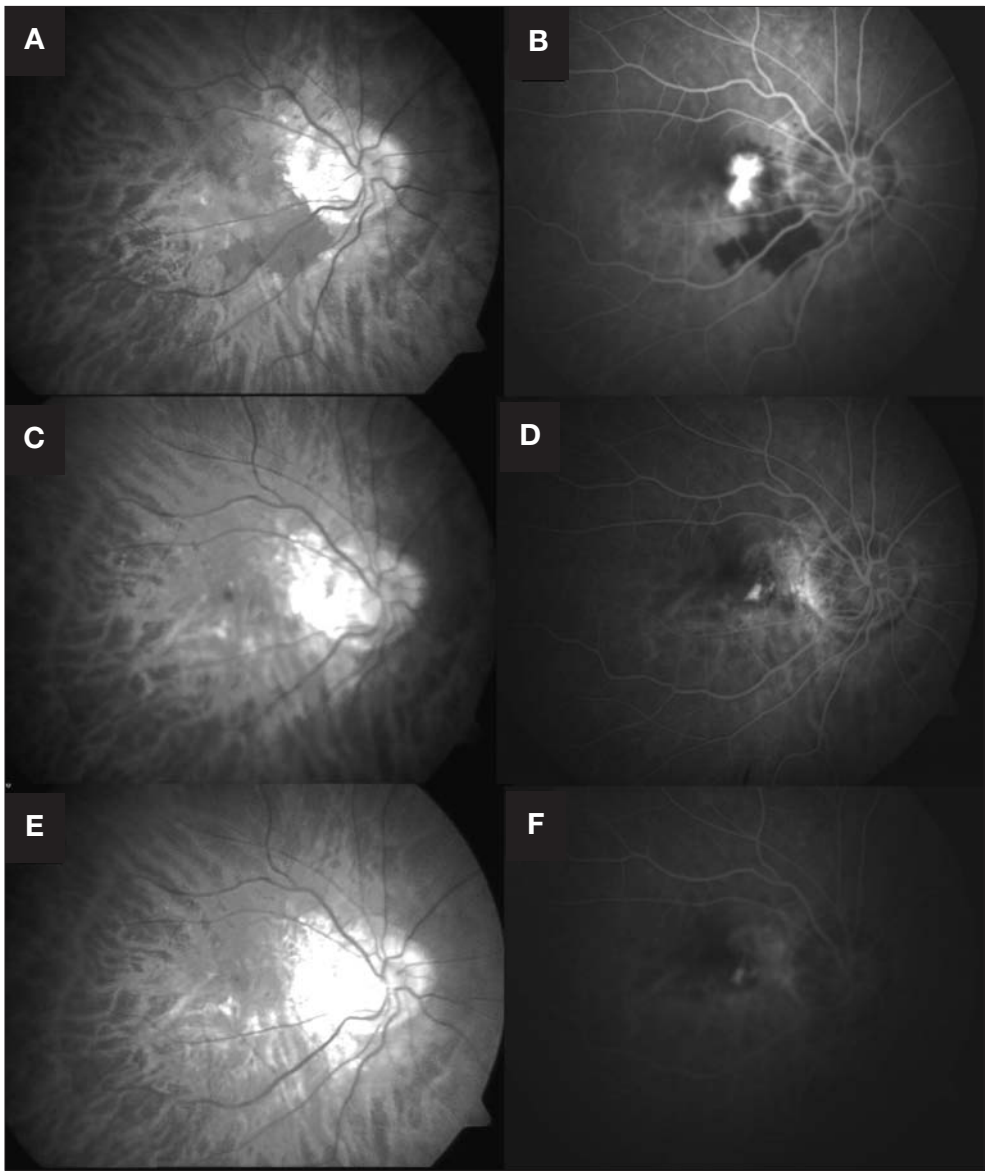

Fig. 1 - (A, B) *Preinjection fundus photograph and fluorescein angiogram showing classic choroidal neovascularization along with subretinal hemorrhage in a 30-year-old female patient with –16 diopters of myopia. Contraction of neovascular membrane and reduced leakage after single injection of intravitreal bevacizumab (1.25 mg/ 0.05 mL) at 3 months* **(C, D)** *and 6 months* **(E, F)**. *Subretinal hemorrhage also resolved gradually. Best-corrected visual acuity improved from 20/200 at baseline to 20/40 at 6 months follow-up.*

thromboembolic events. The mean blood pressure at baseline and 6 months follow-up were 125/75 and 126/73 mmHg, respectively.

DISCUSSION

Regarding the natural history of mCNV, previously reported studies have conflicting results. Avila et al (7) reported that CNV in high myopia has a relatively self-limited course with favorable visual outcome. However, most other reports show progressive deterioration of vision (8, 9) and emphasize that mCNV should not be left untreated. Yoshida et al (10) showed a characteristic course of visual decline during the 10-year follow-up period. In the initial 3 years, the visual acuity did not decrease significantly but in almost all eyes visual acuity dropped to 20/200 or less within 10 years after the onset.

PDT is the only proven modality in treatment of CNV from various etiologies including high myopia. In the Verteporfin in Photodynamic Therapy (VIP) trial, at 6 months 17.9% of eyes in the placebo arm compared to 16% of eyes in the treatment arm had no leakage on FFA. However, 26% of PDT treated eyes compared with 56% of placebo-treated eyes lost fewer than eight letters on an Early Treatment Diabetic Retinopathy Study (ETDRS)

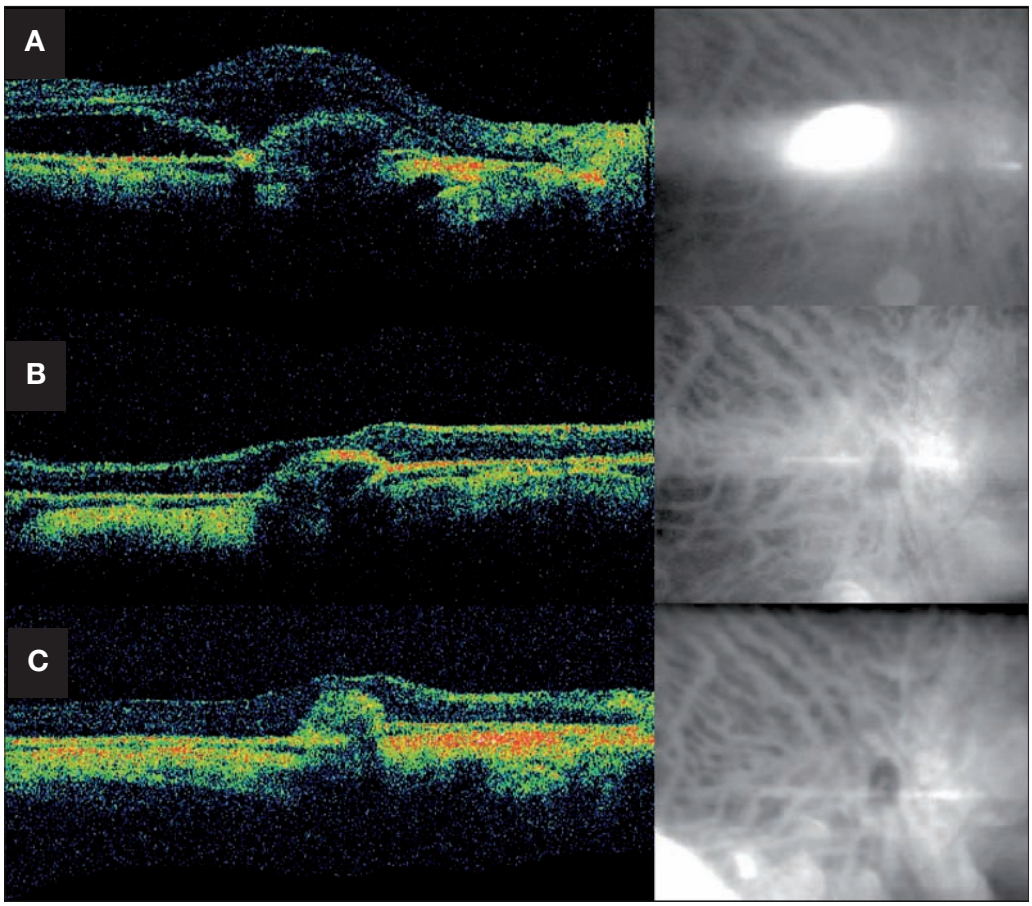

Fig. 2 - (A) *Baseline horizontal line scan (5 mm) showing fusiform choroidal neovascularization (CNV) complex along with subretinal fluid and retinal edema. Follow-up horizontal line scan* **(B, C)** *at 3 and 6 months demonstrates complete resolution of subretinal fluid and reduction of retinal edema. CNV complex has also contracted compared to baseline.*

chart at 6 months. In VIP trial at 1 year, 72% of PDT treated eyes compared with 44% of placebo-treated eyes lost fewer than eight letters on an ETDRS chart but at 2 years the treatment benefit was no longer present (3, 4). On average 5.1 treatments per eye were performed over a 2-year follow-up. In contrast to PDT results at 6 months, only 1 out of 12 eyes lost two or more lines of BCVA in our series. This is suggestive that intravitreal bevacizumab may be more beneficial during short-term follow-up.

Recently, PDT has been combined with intravitreal triamcinolone (IVTA) to reduce the retreatment frequency and improve visual outcomes versus PDT alone (11, 12). No large trial has been done to conclude whether combined PDT and IVTA is a more effective treatment than PDT alone.

Surgical removal of CNV and macular translocation require expertise and have higher complication rates and variable visual results (13, 14).

Although pathogenesis of CNV is elusive, it is well recognized that mediators of angiogenesis have an important role. The most widely studied mediator has been vascular endothelial growth factor (VEGF), which plays a central role in the complex cascade of vessel growth, proliferation, and hyperpermeability. Several anti-VEGF therapies have achieved favorable results in the treatment of CNV due to age-related macular degeneration (AMD).

Bevacizumab (Avastin), a humanized anti-VEGF antibody that inhibits VEGF-A protein, has been reported to cause regression of CNV after intravenous or intravitreal injection secondary to AMD (15-17). After the initial encouraging results; off-level bevacizumab is being tried in different retinal pathologies. Intravenous and intravitreal bevacizumab in mCNV has been reported to be beneficial in a few recent publications. Nguyen et al (18) reported the effectiveness of intravenous injection of bevacizumab (5 mg/kg) to treat subfoveal CNV secondary to pathologic myopia.

In a retrospective chart review of 11 eyes of 9 patients by Yamamoto et al (19), the effect of intravitreal bevacizumab for treating subfoveal CNV secondary to pathologic my-

opia was assessed. They reported a mean of +3.5 lines improvement in VA with 8 eyes achieving 20/50 or better vision at the last follow-up. Of the total of 11 eyes in the study, in 6 eyes intravitreal bevacizumab was used as primary treatment.

Sakaguchi et al (20), in a nonrandomized, interventional case series, treated eight patients with mCNV with intravitreal bevacizumab (1 mg). In six eyes (75%) the BCVA improved two or more lines, and it remained the same in two eyes (25%). Out of eight patients, two had received prior sub-Tenon injection of triamcinolone.

In our small series we have evaluated the efficacy and safety of intravitreal bevacizumab in mCNV as primary treatment modality.

In our study, at the final visit, 8 eyes (67%) had final BCVA of 20/80 or more. The mean improvement in BCVA was +5.1 lines. Yamamoto et al (19) reported a mean of +3.5 lines improvement in VA. In spite of no fluid in OCT, four eyes had poor visual outcome. All of them had large central foveal scar, explaining the visual outcome.

On OCT the mean CMT at baseline was 403.67 µm (median=365 µm). The mean CMT rapidly declined to 243.5 µm (median=245.5 µm) at 4 weeks after single injection. During further follow-up, there was no further significant reduction in mean CMT. At last visit, the mean CMT was 229.41µm (median=239 µm) with average reduction 174.25 µm from baseline. In the series of Yamamoto et al (19), central foveal thickness improved from 340 µm to 234 µm, representing an average reduction of 103 µm. However, Sakaguchi et al (20) found a mean foveal thickness of 198.4 µm before treatment, which declined to 155.1 µm after treatment.

We decided to repeat the injection based on clinical examination and OCT findings. FFA was done at 3-month intervals to document the CNV size and its activity. In our series, five eyes required second injections while one eye required a third injection for resolution of edema, SRF, and/or RPED, as per OCT criteria.

Out of 12 eyes, only one eye developed mild iridocyclitis. However, uveitis has not been reported by others (17, 18). No other complications were observed in our study.

Limitations of our study include small number of patients and short follow-up. Despite this, our observation strongly suggests that intravitreal bevacizumab seems to be effective and safe for the treatment of mCNV. However, long-term safety and efficacy of intravitreal bevacizumab in the treatment of mCNV needs to be evaluated further with long-term follow-up in larger number of patients.

The authors report no financial support or proprietary interest.

Reprint requests to:
Pradeep Venkatesh, MD
Dr. Rajendra Prasad Centre for Ophthalmic Sciences
All India Institute of Medical Sciences
New Delhi, India
venkyprao@yahoo.com

REFERENCES

1. Secretan M, Kuhn D, Soubrane G, Coscas G. Long-term visual outcome of choroidal neovascularization in pathologic myopia: natural history and laser treatment. Eur J Ophthalmol 1997; 7: 307-16.
2. Johnson DA, Yannuzzi LA, Shakin JL, Lightman DA. Lacquer cracks following laser treatment of choroidal neovascularization in pathologic myopia. Retina 1998; 18: 118-24.
3. Verteporfin in Photodynamic Therapy Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in pathologic myopia with verteporfin. 1-year results of a randomized clinical trial–VIP report no. 1. Ophthalmology 2001; 108: 841-52.
4. Verteporfin in Photodynamic Therapy (VIP) Study Group. Verteporfin therapy of subfoveal choroidal neovascularization in pathologic myopia. 2-year results of a randomized clinical trial-VIP report no. 3. Ophthalmology 2003; 110: 667-73.
5. Krebs I, Binder S, Stolba U, Glittenberg C, Brannath W, Goll A. Choroidal neovascularization in pathologic myopia: three-year results after photodynamic therapy. Am J Ophthalmol 2005; 140: 416-25.
6. Ruiz-Moreno JM, de la Vega C. Surgical removal of subfoveal choroidal neovascularisation in highly myopic patients. Br J Ophthalmol 2001; 85: 1041-3.
7. Avila MP, Weiter JJ, Jalkh AE, et al. Natural history of choroidal neovascularization in degenerative myopia. Ophthalmology 1984; 91: 1573-81.

8. Hampton GR, Kohen D, Bird AC. Visual prognosis of disciform degeneration in myopia. Ophthalmology 1983; 90: 923-6.
9. Hotchkiss ML, Fine SL. Pathologic myopia and choroidal neovascularization. Am J Ophthalmol 1981; 91: 177- 83.
10. Yoshida T, Ohno-Matsui K, Yasuzumi K, et al. Myopic choroidal neovascularization. A 10-year follow-up. Ophthalmology 2003; 110: 1297-305.
11. Degenring RF, Jonas JB. Photodynamic therapy in combination with intravitreal triamcinolone for myopic choroidal neovascularization [letter]. Acta Ophthalmol Scand 2005; 83: 621.
12. Potter MJ, Szabo SM, Ho T. Combined photodynamic therapy and intravitreal triamcinolone for the treatment of myopic choroidal neovascularization in a 13-year old girl. Graefes Arch Clin Exp Ophthalmol 2005; 21: 1-3.
13. Hamelin N, Glacet-Bernard A, Brindeau C, et al. Surgical treatment of subfoveal neovascularization in myopia: macular translocation vs. surgical removal. Am J Ophthalmol 2002; 133: 530-6.
14. Bottoni F, Perego E, Airaghi P, et al. Surgical removal of subfoveal choroidal neovascular membranes in high myopia. Graefes Arch Clin Exp Ophthalmol 1999; 237: 573-82.
15. Michels S, Rosenfeld PJ, Puliafito CA, Marcus EN, Venkatraman AS. Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration twelve-week results of an uncontrolled open-label clinical study. Ophthalmology 2005; 112: 1035-47.
16. Avery RL, Pieramici DJ, Rabena MD, et al. Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. Ophthalmology 2006; 113: 363-72.
17. Bashshur ZF, Bazarbachi A, Schakal A, et al. Intravitreal bevacizumab for the management of choroidal neovascularization in age-related macular degeneration. Am J Ophthalmol 2006; 142: 1-9.
18. Nguyen QD, Shah S, Tatlipinar S, et al. Bevacizumab suppresses choroidal neovascularisation caused by pathological myopia. Br J Ophthalmol 2005; 89: 1368-70.
19. Yamamoto I, Rogers AH, Reichel E, Yates P, Duker JS. Intravitreal bevacizumab (Avastin) as treatment for subfoveal choroidal neovascularization secondary to pathologic myopia. Br J Ophthalmol 2007; 91: 157-60.
20. Sakaguchi H, Ikuno Y, Gomi F, et al. Intravitreal injection of bevacizumab for choroidal neovascularization caused by pathological myopia. Br J Ophthalmol 2007; 91: 161-5.