DOI:10.14744/bej.2018.88598
Beyoglu Eye J 2018; 3(1): 8-12

Original Article

Intravitreal Ranibizumab Therapy for Choroidal Neovascularization Secondary to Pathological Myopia: 3-Year Outcomes

Irfan Perente,[1] Ozgur Artunay,[1] Alper Sengul[2]

[1]Department of Ophthalmology, Beyoglu Eye Training and Research Hospital, Istanbul, Turkey
[2]Department of Ophthalmology, T.C. Istanbul Bilim University Faculty of Medicine, Istanbul, Turkey

Abstract

Objectives: The purpose of this study was to report the functional and anatomical results of intravitreal ranibizumab (IVR) injections administered for myopic choroidal neovascularization (mCNV) secondary to pathological myopia.

Methods: In this retrospective study, 32 eyes of 32 mCNV patients were evaluated. After a first IVR injection, patients were followed up and treated with an as-needed monthly regime. Best-corrected visual acuity and optic coherence tomography (OCT) findings were evaluated at baseline and then monthly. The reinjection criteria were a reduction in visual acuity and/or an increase in central macular thickness measured with OCT.

Results: The mean age of the patients was 57.7±14.6 years, and the mean axial length was 27.8±1.3 mm. The mean visual acuity improved significantly from 46.4±9.7 letters at baseline to 54.1±9.5 letters at the last follow-up visit ($p<0.05$). The mean central macular thickness decreased from 301.4±11.7 μm at baseline to 258.8±12.5 μm at the last visit ($p>0.05$). The mean number of injections was 3.5±1.1, 2.3±0.9, and 1.7±0.8, at 12, 24, and 36 months, respectively.

Conclusion: The results of this study indicated that IVR injections provided a significant long-term visual and anatomical benefit in cases of mCNV with few injections.

Keywords: Central macular thickness, intravitreal ranibizumab, myopic choroidal neovascularization.

Introduction

High degree myopia is a major cause of legal blindness in many developed countries (1-3). It affects 27% to 33% of all myopic eyes, corresponding to a prevalence of 1.7% to 2% in the general population (4). High myopia is defined as a refractive error of at least -6.00 D or an axial length of 26.5 mm or more. Pathological or degenerative myopia is defined as high myopia with any posterior myopia-specific pathology from axial elongation. A proportion of people with myopia have pathological myopia, which is characterized by excessive and progressive elongation of the globe, and is now considered to be an important cause of impaired vision and blindness worldwide (3, 4).

Myopic choroidal neovascularization (mCNV) may develop in 5% to 10% of people with pathological myopia, and is mainly characterized by widespread chorioretinal degeneration in the posterior pole of the eye, the growth of new blood vessels from the choroid capillary layer, breaks of Bruch's membrane, subsequent subretinal hemorrhage, and fibrotic membrane formation under the foveola (5-7). Mechanical, heredodegenerative, and hemodynamic theories have been proposed to explain the development of mCNV (8-12).

Before the era of intravitreal anti-vascular endothe-

Address for correspondence: Alper Sengul, MD. Department of Ophthalmology, T.C. Istanbul Bilim University Faculty of Medicine, Istanbul, Turkey
Phone: +90 212 224 49 50 **E-mail:** ealper_sengul@yahoo.com
Submitted Date: January 15, 2018 **Accepted Date:** March 14, 2018 **Available Online Date:** April 04, 2018

lial growth factor (VEGF) drugs (bevacizumab, pegaptanib sodium, ranibizumab and aflibercept), laser photocoagulation, verteporfin photodynamic therapy, and surgical excision or macular translocation were performed to treat mCNV (13-16). The results of the REPAIR (Phase 2) and the RADIANCE (Phase 3) studies demonstrated good visual gain and anatomical improvement with intravitreal ranibizumab (IVR) (17-18). The efficacy and safety of IVR for mCNV have been demonstrated in several small prospective and retrospective studies (19-22). There are a few reports on long-term outcomes of anti-VEGF therapy in mCNV in the literature (23-25).

The aim of this study was to report the long-term anatomical and visual outcomes of IVR monotherapy in naive CNV caused by myopia.

Methods

This study was a retrospective assessment of the records of 32 eyes of 32 consecutive patients who were given IVR. They were all diagnosed with mCNV and followed up for 3 years, with additional treatment provided on an as-needed basis. The study was approved by the ethics committee of Istanbul Bilim University. Written informed consent was obtained from each patient in accordance with the ethical principles stated in the Declaration of Helsinki.

The inclusion criteria were eyes with a myopic refractive error (spherical equivalent) ≥8.0 D or an axial length ≥26.0 mm, treatment naive mCNV, leakage of fluorescein from the CNV during fluorescein angiography, treated with anti-VEGF monotherapy, and a minimum follow-up period of 3 years after the first IVR treatment. Patients were excluded if they had CNV due to another etiology, any ocular disease other than pathologic myopia, any concurrent ocular disease in the study eye that could be the cause of vision loss; chronic ocular disease (uveitis and optic neuritis); open-angle glaucoma, angle-closure glaucoma, or suspected glaucoma; optic nerve disease (anterior ischemic optic neuropathy); neurological disease (multiple sclerosis); a history of other treatment for CNV; or a follow-up period of fewer than 36 months.

The IVR (Lucentis; Novartis Pharma AG, Basel, Switzerland) was injected at a dose of 0.5 mg/0.05 mL once per month for 3 consecutive months. The decision to administer further injections was made on an as-needed basis. At each visit, the best-corrected visual acuity (BCVA) was measured using the ETDRS scale. Each visit also incorporated a biomicroscopic examination of the anterior segment, measurement of intraocular pressure (IOP), a fundus examination, and a central macular thickness (CMT) measurement using optical coherence tomography (OCT) (Optovue , Inc., Fremont, CA, USA). The decision to administer subsequent injections was based on the BCVA and CMT results for each patient. The following criteria were considered when making a decision about reinjection: persistence or recurrence of subretinal fluid or cystic structures via OCT, an increase in the most recent OCT measurement of CMT of 50 μm or more, incipient CNV, incipient hemorrhage, and a loss of 5 or more letters when compared with the last recorded BCVA.

The intraocular injections were carried out under operating theater conditions. Following topical application of proparacaine, the eyelids, lashes, and conjunctiva were cleaned with 5% povidone iodine. After placement of a speculum to keep the eyelids open, IVR was injected at a distance of 4 mm from the superior temporal quadrant. After the injection, the patient was given a topical antibiotic in the quinolone group to use 4 times each day for a period of 7 days.

Biochemical values were measured at the first visit and after every 12 months, and hematology, blood chemistry, and urine were regularly monitored. IOP measurement (before and after each administration, using tonometry) and a standard ophthalmic examination were also performed at every visit.

The values are presented as the mean±SD. The Student's t-test or the Mann–Whitney U test was used to determine the significance of the differences in the BCVA, and CMT value recorded. A P value <0.05 was considered statistically significant.

Results

The mean age of the study patients was 57.7±14.6 years. Fourteen patients were men and 18 were women. All of the eyes were naive and all of the patients were treated with anti-VEGF monotherapy with IVR. The mean refractive error was -12.8±4.5 and the mean axial length was 27.8±1.3 mm (Table 1).

The mean number of ETDRS letters read was 46.4±9.7 at baseline, 53.2±10.9 at 6 months, 54.4±9.9 at 12 months, 54.3±8.8 at 18 months, 54.4±9.9 at 24 months, 54.2±10.1 at 30 months, and 54.1±9.5 at 36 months ($p<0.005$; baseline vs 6, 12, 18, 24, and 36 months). A BCVA improvement of ≥15 letters was seen in 9 (28.1%), 10 (31.2%), and 9 (28.1%) eyes at 12, 24, and 36 months, respectively. (Fig. 1) Furthermore, a BCVA improvement of >5 letters was determined in 20 (62.5%), 20 (62.5%), and 17 (53.1%) eyes at 12, 24, and 36

Table 1. Clinical characteristics of study patients

Age (years)	57.7±14.6
Sex (male/female)	14/18
Eye (right/left)	17/15
Spherical equivalent (D)	-12.8±4.5
Axial length (mm)	27.8±1.3

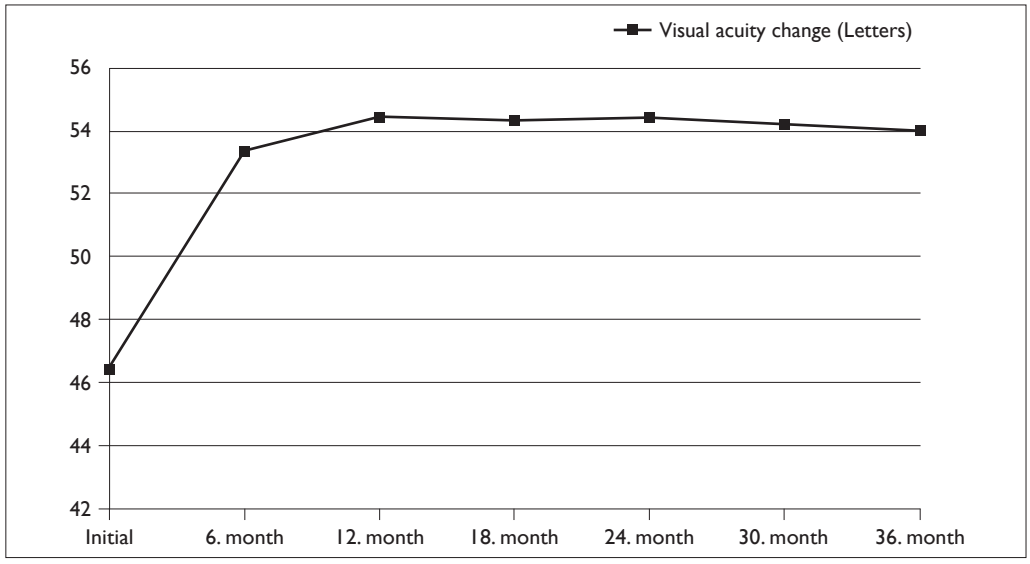

Figure 1. Change in mean best-corrected visual acuity at month 36 after intravitreal ranibizumab treatment.

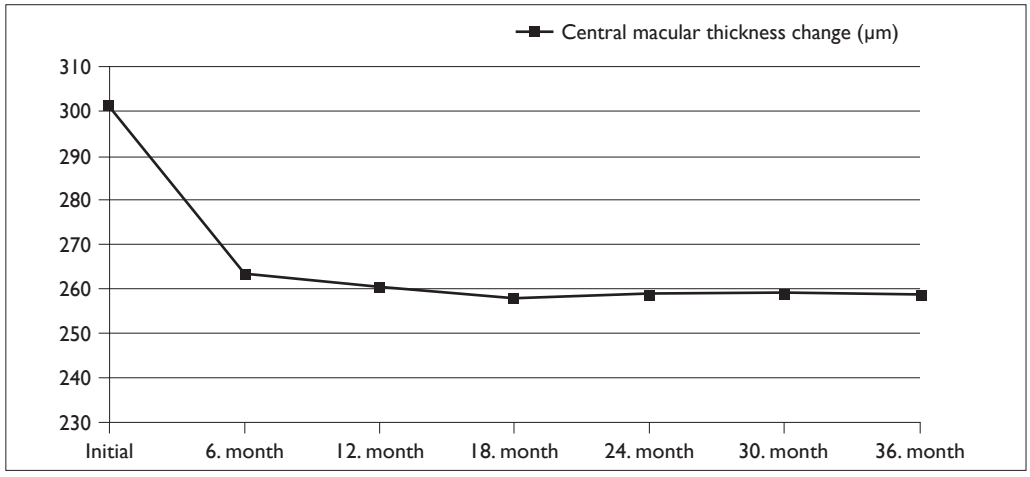

Figure 2. Change in mean central macular thickness at month 36 after intravitreal ranibizumab treatment.

months, respectively. A BCVA deterioration of >5 letters was observed in 3 (9.3%), 3 (9.3%), and 4 (12.5%) eyes at 12, 24, and 36 months, respectively.

The mean CMT was 301.4±11.7 μm at baseline, 264.7±10.9 μm at 6 months, 260.7±13.9 μm at 12 months, 258.4±11.5 μm at 18 months, 258.6±10.9 μm at 24 months, 258.6±10.1 μm at 30 months, and 258.8±12.5 μm at 36 months ($p<0.005$; baseline vs 6, 12, 18, 24, and 36 months). (Fig. 2)

The mean number of injections administered was 3.5±1.1, 2.3±0.9, and 1.7±0.8 at the first, second, and third year, respectively. (Fig. 3)

Discussion

The prevalence of myopia and high myopia has been increasing globally at an alarming rate, with significant increases in terms of the risks for vision impairment due to pathological conditions. High myopia was estimated to affect 2.8% (170 million) of the world population in 2010. Preliminary projections were based on these prevalence data and the corresponding population figures of United Nations. Considering the effects of age and time, we may assume that high myopia will affect 10.0% (925 million) of the world population by 2050 (26).

The reported prevalence of pathological myopia based on population studies is 1% to 3% in adults, and 5% to 11% of those patients with pathological myopia develop mCNV. Several phenotypic features of pathological myopia are associated with an increased risk for mCNV; they include lacquer cracks, patchy atrophy, thinning of the choriocapillaris and choroid, and mCNV in the fellow eye (9, 12, 27). Long-term studies of the natural course of pathological myopia have reported that almost all patients have significant vision loss (28-30). In a 10-year follow-up of 25 patients with mCNV, visual acuity was found to be <20/200 in 89% of the patients

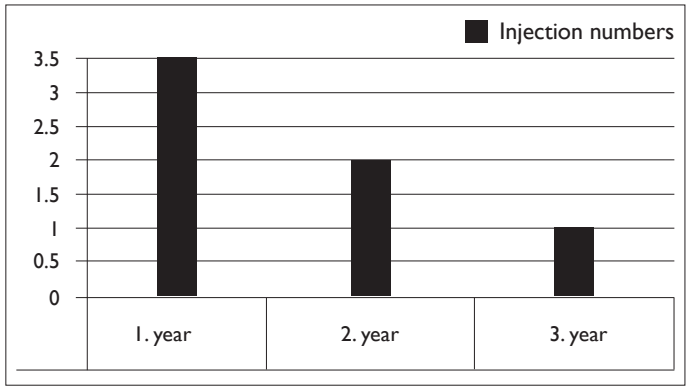

Figure 3. Mean number of intravitreal injections administered over 3 years.

5 years after onset, and in 96% 10 years after the onset of CNV (31).

In a prospective, interventional study of 19 highly myopic eyes of 18 patients with subfoveal and juxtafoveal CNV who were treated with intravitreal bevacizumab on a pro re nata (PRN) regimen after 3 loading injections, Ruiz-Moreno et al. (32) reported that the initial BCVA gain had decreased and was no longer significant by the end of the second year. However, these results could be related to the relatively small sample size and short follow-up period of the study. On the other hand, Gharbiya et al. (33) and Nakanishi et al. (34) demonstrated that intravitreal bevacizumab for mCNV led to a rapid and sustained visual and anatomical improvement over 2 years.

In a phase 3, 12-month, randomized, multicenter study of IVR in patients with mCNV, IVR was administered according to the presence/absence of CNV activity in 1 group and according to visual acuity changes in a second group. The RADIANCE study demonstrated that IVR treatment based on CNV activity was as effective as ranibizumab treatment based on visual acuity stability at 6 months (17). In the REPAIR study, Tufail et al. (18) reported that OCT-guided retreatment had excellent efficacy with a small number of injections in mCNV patients. Relying on these findings, a re-treatment regime based on functional parameters assessed with BCVA and morphological parameters assessed with SDOCT appears to be a reliable and effective procedure for mCNV patients.

Franqueira et al. (20) retrospectively analyzed the 3-year safety and efficacy of IVR. The change from baseline BCVA was +4.3 letters at 12 months, +6.4 letters at 24 months, and +8.0 letters at 36 months. Twenty-five percent of the patients gained ≥15 letters at 12 months, 30% at 24 months, and 35% at 36 months. A mean of 4.1 injections was administered in the first year, 2.4 in the second year, and 1.1 in the third year. In our study, the BCVA change was +8.0 letters at 12 months, +8.0 letters at 24 months, and +7.7 letters at 36 months. The BCVA gain was greater in the first year, and this gain was maintained for 3 years.

In a retrospective, nonrandomized study, Ladaique et al. (35) reported functional results concerning the efficacy of IVR for mCNV with a PRN regimen. The mean BCVA improved significantly from 62.8±13.8 letters at baseline to 72.8±12.9 letters at the last follow-up visit. The mean BCVA improvement of ≥15 letters was 21% at 12 months, 18% at month 24, 20% at month 36, and 22% at month 48 (35). In our study, a BCVA improvement of ≥15 letters was noted in 28.1%, 31.2%, and 28.1% of eyes at 12, 24, and 36 months, respectively. Our relatively greater percentage of patients gaining ≥15 letters could be explained by the greater mean baseline BVCA of our study group. (62.8 vs 46.4)

In our study, the mean number of injections administered was 3.5±1.1, 2.3±0.9, and 1.7±0.8 injections at 12, 24, and 36 months, respectively. The percentage of eyes given ≤1 injection was 75% at 12 months, 82% at 24 months, and 88% at 36 months. Also, 81% of eyes received a maximum of 3 injections at 36 months. These findings confirmed that fewer injections were needed to achieve stable visual acuity than for other diseases that respond to anti-VEGF.

A retrospective research method and the small number of patients included are limitations of this study. The lack of control group for analysis of treatment decision specificity is also a limitation.

In conclusion, our study reports long-term safety and benefits of IVR monotherapy in the treatment of mCNV on a PRN regimen and confirms an excellent long-term visual prognosis with a small number of injections. However, randomized studies with long-term outcomes and a larger sample size are warranted.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Involved in design and conduct of the study (IP, OA, AS); preparation and review of the study (AS); data collection (IP, OA, AS); and statistical analysis (OA, AS).

References

1. Wong TY, Ferreira A, Hughes R, Carter G, Mitchell P. Epidemiology and disease burden of pathologic myopia and myopic choroidal neovascularization: an evidence-based systematic review. Am J Ophthalmol 2014;157:9–25.e12. [CrossRef]
2. Chan NS, Teo K, Cheung CM. Epidemiology and Diagnosis of Myopic Choroidal Neovascularization in Asia. Eye Contact Lens 2016;42:48–55. [CrossRef]
3. Neelam K, Cheung CM, Ohno-Matsui K, Lai TY, Wong TY. Choroidal neovascularization in pathological myopia. Prog Retin Eye Res 2012;31:495–525. [CrossRef]
4. Ohno-Matsui K. What is the fundamental nature of pathologic myopia? Retina 2017;37:1043–8. [CrossRef]

5. Ohno-Matsui K, Lai TY, Lai CC, Cheung CM. Updates of pathologic myopia. Prog Retin Eye Res 2016;52:156–87. [CrossRef]
6. Miller DG, Singerman LJ. Natural history of choroidal neovascularization in high myopia. Curr Opin Ophthalmol 2001;12:222–4.
7. Gelisken O, Yalcinbayir O. Retinal Findings and Complications in Pathological Myopia. Ret-Vit 2010;18:108-113.
8. Seko Y, Seko Y, Fujikura H, Pang J, Tokoro T, Shimokawa H. Induction of vascular endothelial growth factor after application of mechanical stress to retinal pigment epithelium of the rat in vitro. Invest Ophthalmol Vis Sci 1999;40:3287–91.
9. Ohno-Matsui K, Yoshida T, Futagami S, Yasuzumi K, Shimada N, Kojima A, et al. Patchy atrophy and lacquer cracks predispose to the development of choroidal neovascularisation in pathological myopia. Br J Ophthalmol 2003;87:570–3. [CrossRef]
10. Neelam K, Cheung CM, Ohno-Matsui K, Lai TY, Wong TY. Choroidal neovascularization in pathological myopia. Prog Retin Eye Res 2012;31:495–525. [CrossRef]
11. Leveziel N, Yu Y, Reynolds R, Tai A, Meng W, Caillaux V, et al. Genetic factors for choroidal neovascularization associated with high myopia. Invest Ophthalmol Vis Sci 2012;53:5004–9.
12. Wakabayashi T, Ikuno Y. Choroidal filling delay in choroidal neovascularisation due to pathological myopia. Br J Ophthalmol 2010;94:611–5. [CrossRef]
13. Ruiz-Moreno JM, Montero JA. Long-term visual acuity after argon green laser photocoagulation of juxtafoveal choroidal neovascularization in highly myopic eyes. Eur J Ophthalmol 2002;12:117–22. [CrossRef]
14. Virgili G, Menchini F. Laser photocoagulation for choroidal neovascularisation in pathologic myopia. Cochrane Database Syst Rev 2005:CD004765. [CrossRef]
15. Özdemir H, Karaçorlu M. Photodynamic Therapy in Patients With Subfoveal Choroidal Neovascularization Secondary to the Pathologic Myopia. Turk J Ophthalmol 2002; 32:769–74
16. Altan T, Acar N, Kapran Z, Unver YB, Ozdogan S. Outcome of photodynamic therapy in choroidal neovascularization due to pathologic myopia and related factors. Int Ophthalmol 2012;32:119–25. [CrossRef]
17. Wolf S, Balciuniene VJ, Laganovska G, Menchini U, Ohno-Matsui K, Sharma T, et al; RADIANCE Study Group. RADIANCE: a randomized controlled study of ranibizumab in patients with choroidal neovascularization secondary to pathologic myopia. Ophthalmology 2014;121:682–92.e2. [CrossRef]
18. Tufail A, Narendran N, Patel PJ, Sivaprasad S, Amoaku W, Browning AC, et al. Ranibizumab in myopic choroidal neovascularization: the 12-monthresults from the REPAIR study. Ophthalmology 2013;120:1944–5.e1. [CrossRef]
19. Calvo-Gonzalez C, Reche-Frutos J, Donate J, Fernandez-Perez C, Garcia-Feijoo J. Intravitreal ranibizumab for myopic choroidal neovascularization: factors predictive of visual outcome and need for retreatment. Am J Ophthalmol 2011;151:529–34.
20. Franqueira N, Cachulo ML, Pires I, Fonseca P, Marques I, Figueira J, et al. Long-term follow-up of myopic choroidal neovascularization treated with ranibizumab. Ophthalmologica 2012;227:39–44. [CrossRef]
21. Lai TY, Luk FO, Lee GK, Lam DS. Long-term outcome of intravitreal anti-vascular endothelial growth factor therapy with bevacizumab or ranibizumab as primary treatment for subfoveal myopic choroidal neovascularization. Eye (Lond) 2012;26:1004–11.
22. Silva RM, Ruiz-Moreno JM, Rosa P, Carneiro A, Nascimento J, Rito LF, et al. Intravitreal ranibizumab for myopic choroidal neovascularization: 12-month results. Retina 2010;30:407–12.
23. Kasahara K, Moriyama M, Morohoshi K, Yoshida T, Simada N, Nagaoka N, et al. Six-year outcomes of intravitreal bevacizumab for choroidal neovascularization in patients with pathologic myopia. Retina. Retina 2017;37:1055–64. [CrossRef]
24. Ladaique M, Dirani A, Ambresin A. Long-term follow-up of choroidal neovascularization in pathological myopia treated with intravitreal ranibizumab. Klin Monbl Augenheilkd 2015;232:542–7. [CrossRef]
25. Wu TT, Kung YH. Five-year outcomes of intravitreal injection of ranibizumab for the treatment of myopic choroidal neovascularization. Retina 2017;37:2056–61. [CrossRef]
26. Holden BA, Fricke TR, Wilson DA, Jong M, Naidoo KS, Sankaridurg P, et al. Global Prevalence of Myopia and High Myopia and Temporal Trends from 2000 through 2050. Ophthalmology 2016;123:1036–42. [CrossRef]
27. Ikuno Y, Jo Y, Hamasaki T, Tano Y. Ocular risk factors for choroidal neovascularization in pathologic myopia. Invest Ophthalmol Vis Sci 2010;51:3721–5. [CrossRef]
28. Kojima A, Ohno-Matsui K, Teramukai S, Ishihara Y, Shimada N, Yoshida T, et al. Estimation of visual outcome without treatment in patients with subfoveal choroidal neovascularization in pathologic myopia. Graefes Arch Clin Exp Ophthalmol 2006;244:1474–9. [CrossRef]
29. Yoshida T, Ohno-Matsui K, Ohtake Y, Takashima T, Futagami S, Baba T, et al. Long-term visual prognosis of choroidal neovascularization in high myopia: a comparison between age groups. Ophthalmology 2002;109:712–9. [CrossRef]
30. Hayashi K, Ohno-Matsui K, Yoshida T, Kobayashi K, Kojima A, Shimada N, et al. Characteristics of patients with a favorable natural course of myopicchoroidal neovascularization. Graefes Arch Clin Exp Ophthalmol 2005;243:13–9. [CrossRef]
31. Yoshida T, Ohno-Matsui K, Yasuzumi K, Kojima A, Shimada N, Futagami S, et al. Myopic choroidal neovascularization: a 10-year follow-up. Ophthalmology 2003;110:1297–305. [CrossRef]
32. Ruiz-Moreno JM, Montero JA. Intravitreal bevacizumab to treat myopic choroidal neovascularization: 2-year outcome. Graefes Arch Clin Exp Ophthalmol 2010;248:937–41. [CrossRef]
33. Gharbiya M, Allievi F, Conflitti S, Esposito M, Scavella V, Moramarco A, et al. Intravitreal bevacizumab for treatment of myopic choroidal neovascularization: the second year of a prospective study. Clin Ter 2010;161:e87–93.
34. Nakanishi H, Tsujikawa A, Yodoi Y, Ojima Y, Otani A, Tamura H, et al. Prognostic factors for visual outcomes 2-years after intravitreal bevacizumab for myopic choroidal neovascularization. Eye (Lond) 2011;25:375–81. [CrossRef]
35. Ladaique M, Dirani A, Ambresin A. Long-term follow-up of choroidal neovascularization in pathological myopia treated with intravitreal ranibizumab. Klin Monbl Augenheilkd 2015;232:542–7. [CrossRef]