Ranibizumab therapy for predominantly hemorrhagic neovascular age-related macular degeneration

Ozlem Dikmetas, Sibel Kadayifcilar, Bora Eldem, Ulkar Feyzullayeva
Department of Ophthalmology, Hacettepe University Faculty of Medicine, Ankara, Turkey

ABSTRACT

OBJECTIVE: Predominantly hemorrhage represents one of the possible manifestations of choroidal neovascularisation (CNV) in eyes with age-related macular degeneration (AMD). The purpose of this study is to evaluate the efficacy of ranibizumab treatment in patients with predominantly hemorrhagic CNV secondary to AMD.

METHODS: Twenty-five patients with predominantly hemorrhagic choroidal neovascularization due to AMD with at least three ranibizumab injections and followed up for at least 12 months were included in the study. The months of follow-up were recorded (baseline, 3rd, 6th, and 12th months). The change in central macular thickness (CMT) on optical coherence tomography, visual acuity (VA) in ETDRS letters, and lesion size on fundus fluorescein angiography were evaluated.

RESULTS: The mean age of the patients was 68.1±5.7 (range: 63–82) years, the mean follow-up was 19.9±14.5 (range: 12–67) months, and the mean number of injections was 4.0±1.4 (range: 3–15). The initial VA was 39.3±17.9 (range: 1–65) letters, CMT was 272.7±104 (range: 164–587) μm, and the initial lesion width was 11.4±10.5 (range: 1.3–45.7) mm². The VA was 41.4±20.1 (range: 5–75) and 36.9±21.8 (range: 4–80) letters (p=0.150), CMT was 270.7±110 (range: 159–570) and 230.4±108 (range: 109–667) μm (p=0.009) and the lesion width was 10.9±11.5 (range: 1.1–39.7) and 10.4±11.6 (range: 1.2–44.3) mm² at 6th and 12th month, respectively. No factor was found to be associated with final CMT.

CONCLUSION: Although the final visual outcome is limited by the progression of the disease, hemorrhagic lesions treated with ranibizumab have stable anatomical outcome.

Keywords: Age-related macular degeneration; hemorrhagic; ranibizumab.

Cite this article as: Dikmetas O, Kadayifcilar S, Eldem B, Feyzullayeva U. Ranibizumab therapy for predominantly hemorrhagic neovascular age-related macular degeneration. North Clin Istanb 2022;9(2):173–179.
differences in terms of vision improvement without the treatment of the underlying haemorrhage [13]. The present study sought to determine the effect of ranibizumab on predominantly hemorrhagic neovascular AMD.

**MATERIALS AND METHODS**

Following Hacettepe University Faculty of Medicine Ethics Board approval (GO 18/90-21, 31.01.2018), data of patients who were treated in University School of Medicine Department of Ophthalmology’s Retina Unit. treatment for hemorrhagic nAMD between 2006 and 2017 were collected, retrospectively. The study was conducted according to the Declaration of Helsinki Principles. Patients with hemorrhagic CNV lesions secondary to nAMD and with at least 1 year of follow-up were included in the study. The other inclusion criteria were being at least 50 years of age and ≥50% of the lesion being hemorrhagic (as defined in the Macular Photocoagulation Study) [14, 15]. Hemorrhagic AMD was defined as ≥50% of the lesion being hemorrhagic with optical coherence tomography (OCT) or clinical fundus examination. The exclusion criteria for the study were the presence of CNV due to other eye diseases (e.g. inflammation) and a follow-up period of <1 year. All the patients received intravitreal injections of ranibizumab (0.5 mg/0.05 ml Lucentis; Genentech Inc., San Francisco, CA, USA). The intravitreal injections were given at baseline, at month 1 and at month 2. All eyes were injected in an operating room. Topical anesthesia was obtained, the conjunctiva was irrigated with 2.5% povidone iodine solution followed by scrub of the eyelids and periorbital area. Patients received an intravitreal injection of 0.5 mg ranibizumab via the pars plana, 3.5–4.0 mm posterior to the limbus using a syringe with a 30-gauge needle. After procedure, all patients instilled moxifloxacin for 5 days. After the 3 monthly injections, retreatment was done as needed (PRN) [16], as following: (1) Visual acuity (VA) loss of five letters or more with Early Treatment of Diabetic Retinopathy Study (ETDRS) letters in comparison with the VA of previous visit; (2) fluid or hemorrhage with clinical examination and increase in central thickness in OCT; recurrent fluid or novel fluid accumulation in OCT; (3) newly developed hemorrhage secondary to CNV; or (4) an active nAMD finding on the fundus fluorescein angiography (FFA), indocyanine green angiography (ICGA) or OCT images. The VA (ETDRS letters), the lesion size on the FFA images and the central macular thickness (CMT) on the OCT images were recorded for each patient at baseline as well as the 3rd, 6th, and 12th months and then analyzed. The diameter of the lesion was analyzed using VISUPAC imaging software (Carl Zeiss Meditec AG, Jena, Germany). The CMT was measured on a horizontal and a vertical scan, and it was defined as the distance between the internal limiting membrane and the inner surface of the retinal pigment epithelium (RPE) at the foveal center. These two measurements were analyzed as the CMT. ICGA was performed for the differential diagnosis of polypoidal choroidal vasculopathy which is the most common cause of hemorrhagic CNV. All measurements were done by the same clinicians (OD).

All data were entered into a database and analyzed using the statistical package for social sciences, SPSS version 18 (SPSS Inc., Chicago, IL, USA). Mann Whitney U test and Chi-square test were employed. The association between lesion components (CMT, lesion width) and VA was analyzed Spearman correlation test. Shapiro-Wilk test for normality and graphics (qq plot, boxplot) were evaluated together to decide the distribution of the data (whether they show normal distribution). Frequency and percentage were used in categorical data, mean and standard deviation were used in numerical data. P<0.05 were considered to be statistically significant.

**RESULTS**

Twenty-five eyes of 25 patients were followed for at least 12 months from September 2006 to December 2017 and the resultant data were retrospectively evaluated. The mean age of the patients was 68.1±5.7 years (range: 63–82 years) and 48% of them were male (12 male and 13 female). The mean number of ranibizumab injections was 4.0±1.4 (range: 3–15) during the entire follow-up peri-
od and 3.8±1.6 (range: 3–9) during the first 12 months. The patients’ ocular characteristics are described in Table 1. The mean follow-up period was 19.9±14.5 months (range: 12–67 months). The mean VA at baseline (ETDRS letters) was 39.3±17.9 letters (range: 1–65 letters). Moreover, the mean CMT at baseline was 272.7±104 µm (range: 164–587 µm), while the mean lesion width at baseline was 11.4±10.5 mm² (range: 1.3–45.7 mm²).

At month 3, the mean VA (ETDRS letters) was 42.1±12.3 letters (range: 13–65 letters), the mean CMT was 254.1±120 µm (range: 169–484 µm) and the mean lesion width was 11.7±11.5 mm² (range: 2.6–30 mm²). At month 6, the mean CMT was 270.7±110 µm (range: 159–570 µm), which indicated a non-statistically significant decrease when compared with baseline (p=0.165). Moreover, the mean lesion width at month 6 was 10.9±11.5 mm² (range: 1.1–39.7 mm²), while the mean VA was 41.4±20.1 letters (range: 5–75 letters). The mean lesion width and VA measurements at month 6 were not found to be statistically different from the measurements at baseline (p=0.180 and p=0.134, respectively).

At the 12th month, the mean CMT was 230.4±108 µm (range: 109–667 µm), which indicated a statistically significant decrease when compared with baseline (p=0.009). The mean change in the CMT as shown on the OCT images during the first 12 months is presented in Figure 1. The initial mean lesion width of 10.4±11.6 mm² (range: 1.2–44.3 mm²) was found to be inversely correlated with the final VA (p=0.048, correlation coefficient=−0.371) (Fig. 2). The final mean VA was 36.9±21.8 letters (range: 4–80 letters), which was not statistically significantly different from the initial VA (p=0.150) (Fig. 3, 4).

### Table 1. Ocular characteristics of patients

|                | Baseline | 3rd month | 6th month | 12th month |
|----------------|----------|-----------|-----------|------------|
| VA (ETDRS)±SD, letters (range) | 39.3±17.9 (1–65) | 42.1±22.8 (6–75) | 41.4±20.1 (5–75) | 36.9±21.8 (4–80) |
| Width of lesion±SD (range) mm² | 11.4±10.5 (1.3–45.7) | 11.7±11.5 (2.6–30) | 10.9±11.5 (1.1–39.7) | 10.4±11.6 (1.2–44.3) |
| CMT with OCT±SD (range) µm | 272.7±104 (164–587) | 254.1±120 (169–484) | 270.7±110 (159–570) | 230.4±108 (109–667) |

SD: Standard deviation; VA: Visual acuity; ETDRS: Early treatment of diabetic retinopathy study; CMT: Central macular thickness; OCT: Optical coherence tomography.
Although 15 (60%) patients remained stable throughout the first 12 months, 10 (40%) patients did not respond to the treatment and developed wide scars. The VA was found to have improved by at least 15 letters in three (12%) patients, whereas it was found to have decreased by ≥15 letters in five (25%) patients at the 12-month follow-up point.

One patient developed a mild vitreous hemorrhage at the 5th month (i.e. 2 months after the third injection), although the hemorrhage resolved spontaneously within a month, leaving behind a scar. There were not any complications. No systemic adverse events related to the usage of ranibizumab were recorded during the follow-up period.

**DISCUSSION**

The intravitreal injection of anti-VEGF drugs has become the standard treatment modality for patients with CNV secondary to AMD [11]. As the number of individuals with AMD increases, it is reasonable to expect that the incidence of submacular hemorrhage associated with AMD will also increase. Yet, most prior multicenter controlled and randomized studies have excluded patients with hemorrhages occupying >50% of the lesion [12].

A range of treatments can be used for the management of hemorrhagic AMD, all of which are associated with different outcomes [17]. For instance, when injected into the vitreous cavity, TPA can cause blood toxicity [18]. Hesse et al. [19] found an increase in SRH due to intravitreal TPA injection, while Kimura et al. [20] reported the complete liquefaction of acute SRH prior to surgery for hemorrhage. Heriot treated the SRH with gas and showed in the Vitrectomy meeting [21]. Ohji et al. found better VA to be achieved following the use of intravitreal gas [22, 23]. When SRH persists for longer than 2 weeks, surgical treatment modalities may be applied [13]. SRH could harm the photoreceptors and outer retinal layers [13, 24]. The surgical removal of hemorrhages related to AMD in the eyes is associated with a poor prognosis in terms of the recovery of VA [13]. Current surgical techniques allow for the removal of subretinal blood. The surgical results seen in AMD patients have often revealed a variable improvement in relation to VA, although the final VA has generally been poor in most series. The use of surgical techniques has not been found to increase the chances of stable or improved VA, and such techniques have been found to be associated with a high risk of rhegmatogenous retinal detachment [25]. Machemer et al. [26] analyzed the outcomes of the macular translocation procedure and found only one patient to exhibit increased final VA. Peyman et al. [27] evaluated the impact of an autologous RPE-choroid graft to the subretinal space and found VA to be increased as a result of the treatment. McLaren et al.[28] investigated an alternative way of performing macular translocation although they did not achieve very effective results [29]. Macular translocation had no promising results [29]. In light of these differing and inconclusive results, additional information is required concerning the best clinical approach for the treatment of SRH.

Anti-VEGF therapy represents an important therapeutic choice for the treatment of hemorrhagic AMD [30]. Stifter et al. [31] evaluated the effects of intravitreal bevacizumab treatment for haemorrhagic AMD and found that VA was improved in 100% of
patients and improved by at least three lines in 9.5% of patients. The hemorrhage was found to be reduced at the 4-month follow-up point. The application of ranibizumab for the treatment of nAMD has been investigated in numerous clinical studies [3–5, 11, 32–34], although studies concerning the use of ranibizumab in relation to hemorrhagic AMD remain scarce. Moreover, there have been no randomized controlled trials of anti-VEGF therapy with regard to hemorrhagic AMD. Chang et al. [35] assessed the effect of ranibizumab on seven patients with hemorrhagic AMD and found subfoveal fibrosis to occur. In the present study, we found the patients’ VA to be stable following anti-VEGF monotherapy in 25 eyes with predominantly hemorrhagic nAMD after 12 months of treatment. The baseline VA was not found to be associated with the CMT; however, a small lesion width at baseline was found to be associated with good VA at the 12-month follow-up point. In our study, the lesion width was found to be inversely associated with the final VA, although similar to Chang et al.’s findings, while the CMT decreased, the VA did not increase, possibly due to the occurrence of subretinal fibrosis. In fact, we observed subretinal fibrosis in 10 (40%) patients whose VA did not increase following the treatment. Iacono et al. [36] found that, at the 12-month follow-up point, the mean VA improved significantly and the mean CMT decreased with the progressive resolution of macular bleeding in 22 out of 23 patients who were treated with ranibizumab. Iacono et al. investigated the effect of the baseline VA on patients’ response to ranibizumab treatment and determined that the letter gain was generally inversely correlated with the baseline VA. This finding is similar to the results of the MARINA and ANCHOR studies. Araiz et al. [37] concluded that the intravitreal administration of ranibizumab for the treatment of exudative hemorrhagic AMD significantly improved patients’ VA, decreased the lesion characteristics (drusen, macular hemorrhages, lipid exudates and retinal pigment epithelial detachment [PED]), and reduced the CMT after 12 months. A number of factors, including intraretinal cysts, the epiretinal membrane, and the architecture of the retinal layers, have been found to affect patients’ response to treatment, although the size of the hemorrhage has been found to be the most important factor in relation to poor results [12]. For instance, decreased long-term VA has been found to be associated with the thickness of the macular haemorrhage [12]. Avery et al. [38] described 41 eyes of 40 patients with hemorrhagic AMD who were followed up without surgical intervention. The authors found significant correlation between the initial size of the hemorrhage and the visual outcome at the 12- and 36-month follow-up points. In the present study, we observed similar results in terms of the initial lesion width. More specifically, the initial lesion width was found to be inversely correlated with the final VA (p=0.038, r=−0.371). Applying the treat and extend regime could provide more achievements to these results. Treat and extend regime is widely accepted today [39]. Tanaka et al. [40] observed the development of new hemorrhagic vision-threatening lesions during anti-VEGF treatment in three eyes for 3.5 years and in one eye for more than 3.5 years. They concluded that the treatment of hemorrhagic AMD was difficult and that new studies could prove helpful.

It is important to acknowledge that the present study had several limitations. The major limitation of the study is its retrospective design. Moreover, due to the retrospective design, there was no control group included in the study. In addition, the study’s sample size was relatively small.

Conclusion

In conclusion, this study showed that intravitreal ranibizumab treatment could improve the vision and anatomy of hemorrhagic AMD eyes without inducing major adverse effects. As a result, such treatment could be an appropriate non-surgical choice for patients with hemorrhagic AMD or, at least, serve to delay the need for surgical intervention. Further prospective studies involving larger population sizes are suggested to analyze the long-term effects of intravitreal ranibizumab on eyes with hemorrhagic AMD.

Ethics Committee Approval: The Hacettepe University Clinical Research Ethics Committee granted approval for this study (date: 31.01.2018, number: GO 18/90-21).

Conflict of Interest: Dr. Kadayifcilar and Dr. Eldem are investigators for Novartis Clinical Studies.

Financial Disclosure: The authors declared that this study has received no financial support.

Authorship Contributions: Concept – OD, SK, BE; Design – OD, SK, BE; Supervision – OD, SK, BE; Fundings – OD, SK, BE; Materials – OD, SK, UF; Data collection and/or processing – OD, SK, UF; Analysis and/or interpretation – OD, SK, UF; Literature review – OD, SK, UF; Writing – OD, SK, UF; Critical review – OD, SK, BE, UF.
REFERENCES

1. Mitchell P, Liew G, Gopinath B, Wong TY. Age-related macular degeneration. Lancet 2018;392:1147–59.
2. Pauleikhoff D. Neovascular age-related macular degeneration: natural history and treatment outcomes. Retina 2005;25:1065–84.
3. Pedrosa AC, Sousa T, Pinheiro-Costa J, Beato J, Falcão MS, Falcão-Reis F, et al. Treatment of neovascular age-related macular degeneration with anti-VEGF agents: predictive factors of long-term visual outcomes. J Ophthalmol 2017;2017:4263017.
4. Virgili G, Do DV, Bressler NM, Menchini U. New therapies for neovascular age-related macular degeneration: critical appraisal of the current evidence. Acta Ophthalmol Scand 2007;89:6–20.
5. Guo MY, Erminian M, Cheng JZ, Zafari Z, Maberley DAL. One-year effectiveness study of intravitreous ranibizumab in wet (neovascular) age-related macular degeneration: a meta-analysis. Pharmacotherapy 2018;38:197–204.
6. Aras C, Yolar M, Gürsoy H, Yetik H, Akar S, Müftüoğlu G, et al. Macular translocation for the treatment of exudative age-related macular degeneration. Journal of Retina-Vitreous 2006;14.
7. Karaçorlu M, Karaçorlu S, Özdemir H. Twelve months results of photodynamic therapy for classic versus occult choroidal neovascularization in patients with age related macular degeneration. Journal of Retina-Vitreous 2003;11.
8. Karasu B, Erdoğan G. Autologous translocation of the choroid and retina pigment epithelium cells(RPE) in age-related macular degeneration: Monitoring the viability of choroid and RPE patch with indocyanine green angiography(ICGA) and fundus autofluorescence(FAF). Photodynamic Photodyn Ther 2019;28:318–23.
9. Ozkaya A, Ergodan G, Tarakçıoğlu HN. Submacular hemorrhage secondary to age-related macular degeneration managed with vitrectomy, subretinal injection of tissue plasminogen activator, hemorrhage displacement with liquid perfluorocarbon, gas tamponade, and face-down positioning. Saudi J Ophthalmol 2018;32:269–74.
10. Konstantinidis L, Mantel I, Zografas L, Ambresin A. Intravitreal ranibizumab in the treatment of predominantly hemorrhagic lesions in exudative age-related macular degeneration. Klin Monbl Augenheilkd 2011;228:288–92.
11. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, et al; MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419–31.
12. Gale R, Korobelnik JF, Yang Y, Wong TY. Characteristics and predictors of early and delayed responders to ranibizumab treatment in neovascular age-related macular degeneration: a retrospective analysis from the ANCHOR, MARINA, HARBOR, and CATT trials. Ophthalmologica 2016;236:193–200.
13. Bressler NM, Bressler SB, Childs AL, Haller JA, Hawkins BS, Lewis H, et al; Submacular Surgery Trials (SST) Research Group. Surgery for hemorrhagic choroidal neovascular lesions of age-related macular degeneration: ophthalmic findings; SST report no. 13. Ophthalmology 2004;111:1993–2006.
14. Fine SL, Hawkins B, Maguire M. Macular photocoagulation study. Arch Ophthalmol 1984;102:1583.
15. Sabates FN, Lee KY, Ziemianski MC, Sabates R. Macular photocoagulation. Arch Ophthalmol 1984;102:1120.
16. Schmidt-Erfurth U, Eldem B, Guymer R, Korobelnik JF, Schlingmann RO, Axer-Siegel R, et al; EXCITE Study Group. Efficacy and safety of monthly versus quarterly ranibizumab treatment in neovascular age-related macular degeneration: the EXCITE study. Ophthalmology 2011;118:831–9.
17. Stanescu-Segall D, Balta F, Jackson TL. Submacular hemorrhage in neovascular age-related macular degeneration: A synthesis of the literature. Surv Ophthalmol 2016;61:18–32.
18. Lüke M, Januszowski K, Warga M, Beutel J, Leitritz M, Gelisken F, et al; Tuuebingen Bevacizumab Study Group. The retinal tolerance to bevacizumab in co-application with a recombinant tissue plasminogen activator. Br J Ophthalmol 2007;91:1077–82.
19. Hesse L, Schroeder B, Heller G, Kroll P. Quantitative effect of intravitreally injected tissue plasminogen activator and gas on subretinal hemorrhage. Retina 2000;20:500–5.
20. Kimura AE, Reddy CV, Folk JC, Farmer SG. Removal of subretinal hemorrhage facilitated by preoperative intravitreal tissue plasminogen activator. Retina 1994;14:83–4.
21. Heriot WJ. Thermofusion of the retina with the RPE to seal tears during retinal detachment repair. Graefes Arch Clin Exp Ophthalmol 2016;254:691–6.
22. Fang IM, Lin YC, Yang CH, Yang CM, Chen MS. Effects of intravitreal gas with or without tissue plasminogen activator on submacular haemorrhage in age-related macular degeneration. Eye (Lond) 2009;23:397–406.
23. Ohji M, Saito Y, Hayashi A, Lewis JM, Tano Y. Pneumatic displacement of subretinal hemorrhage without tissue plasminogen activator. Arch Ophthalmol 1998;116:1326–32.
24. Gök M, Karaağaç VL, Aşlan MS, Kara Ö, Karaman S, Yenihayat F. Tissue plasminogen activator-assisted vitrectomy for submacular hemorrhage due to age-related macular degeneration. Indian J Ophthalmol 2017;65:482–7.
25. Kamei M, Tano Y, Maeno T, Ikuno Y, Mitsuda H, Yuasa T. Surgical removal of submacular hemorrhage using tissue plasminogen activator and perfluorocarbon liquid. Am J Ophthalmol 1996;121:267–75.
26. Machemer R, Seinhorst UH. Retinal separation, retinotomy, and macular relocation: II. A surgical approach for age-related macular degeneration? Graefes Arch Clin Exp Ophthalmol 1993;231:635–41.
27. Peyman GA, Blinder KJ, Paris CL, Alturki W, Nelson NC Jr, Desai U. A technique for retinal pigment epithelium transplanation for age-related macular degeneration secondary to extensive subfoveal scarring. Ophthalmic Surg 1991;22:102–8.
28. MacLaren RE, Bird AC, Sathia PJ, Aylward GW. Long-term results of submacular surgery combined with macular translocation of the retinal pigment epithelium in neovascular age-related macular degeneration. Ophthalmology 2005;112:2081–7.
29. van Meurs JC, Van Den Biesen PR. Autologous retinal pigment epithelium transplantation and choroid translocation in patients with exudative age-related macular degeneration: short-term follow-up. Am J Ophthalmol 2003;136:688–95.
30. Aisenbrey S, Ziemanssen F, Völker M, Gelisken F, Szurman P, Jaisle G, et al. Intravitreal bevacizumab (Avastin) for occult choroidal neovascularization in age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol 2007;245:941–8.
31. Stifter E, Michels S, Prager F, Georgopoulos M, Polak K, Hirn C, et al. Intravitreal bevacizumab therapy for neovascular age-related macular degeneration with large submacular hemorrhage. Am J Ophthalmol 2007;144:886–92.
32. Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, et al; ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 2006;355:1432–44.
33. Gillies MC, Campain A, Walton R, Simpson JM, Arnold JJ, Guymer RH, et al; Fight Retinal Blindness Study Group. Time to initial cli-
nician-reported inactivation of neovascular age-related macular degeneration treated primarily with ranibizumab. Ophthalmology 2015;122:589–94.
34. Mehta S. Age-related macular degeneration. Prim Care 2015;42:377–91.
35. Chang MA, Do DV, Bressler SB, Cassard SD, Gower EW, Bressler NM. Prospective one-year study of ranibizumab for predominantly hemorrhagic choroidal neovascular lesions in age-related macular degeneration. Retina 2010;30:1171–6.
36. Iacono P, Parodi MB, Introini U, La Spina C, Varano M, Bandello F. Intravitreal ranibizumab for choroidal neovascularization with large submacular hemorrhage in age-related macular degeneration. Retina 2014;34:281–7.
37. Araiz J, Fernandez-Baca I, Roura M, Grupo de Estudio EE. Clinical course of patients with exudative-haemorrhagic age-related macular degeneration treated with ranibizumab. Eye2Eye study. Arch Soc Esp Oftalmol 2013;88:216–22.
38. Avery RL, Fekrat S, Hawkins BS, Bressler NM. Natural history of subfoveal subretinal hemorrhage in age-related macular degeneration. Retina 1996;16:183–9.
39. Silva R, Berta A, Larsen M, Macfadden W, Feller C, Monés J; TREND Study Group. Treat-and-extend versus monthly regimen in neovascular age-related macular degeneration: results with ranibizumab from the TREND study. Ophthalmology 2018;125:57–65.
40. Tanaka E, Chaikitchmongkol V, Bressler SB, Bressler NM. Vision-threatening lesions developing with longer-term follow-up after treatment of neovascular age-related macular degeneration. Ophthalmology 2015;122:153–61.