

Aflibercept in macular edema secondary to retinal vein occlusion: A real life study



Abdullah Ozkaya*; Beril Tulu; Ruveyde Garip

Abstract

Purpose: To evaluate the real life outcomes of intravitreal aflibercept (IVAfl) treatment in patients with macular edema (ME) secondary to retinal vein occlusion (RVO) during the first year of treatment.

Methods: Retrospective case series. Newly diagnosed or persistent ME patients secondary to RVO who were treated with IVAfl and had a follow-up period of at least 12 months were included. Twenty-two patients (54.8%) received 3 loading month loading doses IVAfl initially, whereas 20 patients (45.2%) did not receive. Then the patients were treated on an as-needed treatment regimen. Primary outcome measures of this study included the change in best corrected visual acuity (BCVA) and central retinal thickness (CRT). Secondary outcome measures were the number of visits and injections.

Results: Forty-two eyes of 42 patients were included. Fourteen patients (33.3%) had central RVO, and 28 (66.7%) had branch RVO. Mean BCVA at baseline and month 12 was 0.98 ± 0.58 and 0.82 ± 0.65 LogMAR, respectively ($p = 0.04$). Mean CRT at baseline and month 12 was 511 ± 141 and 304 ± 95 μm , respectively ($p < 0.0001$). Mean number of visits was 5.9 ± 2.1 (range 3–11) and injections was 3.2 ± 1.7 (range 1–8) at month 12.

Conclusion: In conclusion, IVAfl treatment seemed to be effective in patients with ME secondary to RVO with respect to visual and anatomical outcomes in real life. In this study the number of visits and injections was lower than randomized controlled trials, but the functional and anatomical outcomes are probably still acceptable.

Keywords: Aflibercept, Macular edema, Retinal vein occlusion

© 2017 The Authors. Production and hosting by Elsevier B.V. on behalf of Saudi Ophthalmological Society, King Saud University.

This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<https://doi.org/10.1016/j.sjopt.2017.09.009>

Introduction

Retinal vein occlusion (RVO) is the second most common retinal vascular disease after diabetic retinopathy.^{1,2} Macular edema (ME) and vitreous hemorrhage are the frequent reasons for the visual loss in RVO patients.³ Various treatment options have been evaluated in the treatment of ME secondary to RVO such as laser photocoagulation, surgical techniques, and intravitreal injections.^{4–12} Currently, the most popular and preferred treatment option is intravitreal

injections.^{9–12} Anti-vascular endothelial growth factor (anti-VEGF) and steroid injections were shown to be effective in the treatment of ME secondary to RVO. Ranibizumab and aflibercept are the approved anti-VEGF agents.^{1,2,6,8–12} In many prospective randomized trials successful treatment outcomes were reported with both of the drugs.^{8–12} However, these studies had very strict follow-up and treatment criteria which were difficult to accommodate for both of the patients and clinicians. Therefore, the real life practices were different from the randomized clinical trials.^{3,13–15} The real life

Received 6 August 2017; received in revised form 23 September 2017; accepted 25 September 2017; available online 28 September 2017.

Beyoglu Eye Training and Research Hospital, Istanbul, Turkey

* Corresponding author at: Beyoglu Eye Training and Research Hospital, Bereketzade Cami Sok., 34421 Beyoglu, Istanbul, Turkey.
e-mail addresses: abdozkaya@gmail.com (A. Ozkaya), beriltulu@gmail.com (B. Tulu), ruveydegarip@gmail.com (R. Garip).



Peer review under responsibility of Saudi Ophthalmological Society, King Saud University



Production and hosting by Elsevier

Access this article online:
www.saudiophthaljournal.com
www.sciencedirect.com

experience with ranibizumab in the treatment of ME secondary to RVO was evaluated in several studies.^{3,15,16} However, there have been a few studies assessing the outcomes of aflibercept treatment in this regard.^{13,14} In the present study, we aimed to evaluate outcomes of intravitreal aflibercept (IVAfl) in the treatment of ME secondary to RVO, as well as mean number of visits and injection numbers during first year of treatment.

Methods

In this retrospective case series, medical records of patients who had ME secondary to RVO and who underwent IVAfl treatment between June and December of 2015 in our clinic were reviewed. Newly diagnosed treatment naïve RVO patients who had macular edema <3 months on first presentation, or had a persistent ME, and had follow-up of at least 12 months were included. Persistent macular edema was defined as experiencing a partial or no response to any previous treatment options other than IVAfl. Patients who had co-existing retinal disease (such as diabetic retinopathy or epiretinal membrane), or media opacities that could decrease visual acuity (VA) were not included. Written informed consent for treatment was obtained from all patients, and the study adhered to tenets of the Declaration of Helsinki.

Data collected from patients' records included age, gender, type of RVO, ischemic status, best corrected visual acuity (BCVA), and central retinal thickness (CRT) at baseline and months 3, 6, 9, and 12, as well as number of visits and given injections.

All patients underwent standardized examination including measurement of BCVA using a projection chart at 4 m, slit-lamp biomicroscopy and fundus examination, and measurement of intraocular pressure via applanation tonometry. Fluorescein angiography (FA) (HRA-2; Heidelberg Engineering, Heidelberg, Germany), and optical coherence tomography (OCT) imaging (Spectralis; Heidelberg Engineering, Heidelberg, Germany) were performed before treatment. All examinations were repeated at all visits, with exception of FA, which was repeated only when cause of VA deterioration could not be clarified with clinical examination and other imaging methods. Optical coherence tomography was used to measure CRT, which was defined as mean thickness of the neurosensory retina in central 1 mm diameter region, and was computed via OCT mapping software provided with device. Fluorescein angiography was inspected for capillary dropout zones at the fovea and peripheral retina, and for leakage, which were accepted as causes of ME. Type of disease was defined as ischemic RVO if ischemic area was ≥ 5 disc areas in branch retinal vein occlusion (BRVO) patients, or ≥ 10 disc areas in central retinal vein occlusion (CRVO) patients.^{2,4} Panretinal or sectorial photocoagulation were applied to the patients who showed any kind of neovascularization during the follow-up. Panretinal photocoagulation was applied to the CRVO patients who showed neovascularization of the iris or at disc or elsewhere. Sectorial laser photocoagulation was applied to the BRVO patients who showed any kind of neovascularization and the treatment area was covered the entire ischemic area which was detected via FA. Twenty of the 42 patients (47.6%) required panretinal or sectorial laser photocoagulation and none of the patients showed neovascular glaucoma.

All injections were performed under sterile conditions after application of topical anesthesia, use of 10% povidone-iodine (Betadine; Purdue Pharma, Stamford, CT, USA) scrub was used on the lids and lashes, and 5% povidone-iodine was administered on the conjunctival sac. Intravitreal aflibercept 2.0 mg/0.5 ml (Eylea; Bayer, Berlin, Germany) was injected through the pars plana at 3.5 mm posterior to the limbus with a 30-gauge needle. Patients were instructed to return to the hospital if they experienced decreased vision, eye pain, or any new symptoms.

Initially, treatment naïve patients received a loading dose of three consecutive monthly injections, whereas the patients with a recurrent edema did not receive. The patients with recurrent edema previously received various treatments such as grid laser photocoagulation (6/19 patients, 31.5%), intravitreal bevacizumab (6/19 patients, 31.5%), intravitreal ranibizumab (13/19 patients, 68.4%), intravitreal triamcinolone (6/19 patients, 31.5%), and intravitreal dexamethasone implant (8/13 patients, 42.1%) injections. Then, the patients were followed monthly, and a single injection of IVAfl was repeated when the VA decreased by one or more lines from the last visit, or any increase was detected in CRT in OCT images (although planned, it was not possible to perform monthly follow-up visits which was one of the main topics of this real life study). At the beginning of the treatment we planned to perform monthly follow-up visits for the patients. However, as a fact of real life practicing we failed to perform the proper monthly visits because of visit and injection scheduling problems. The visits were performed in an irregular fashion and the time period between the visits varied from 1 to 3 months. The patients were treated with an additional intravitreal dexamethasone implant if there was not a prominent anatomical response (restoration of foveal pit, CRT <350 μ m) after 3 consecutive IVAfl injection.

Primary outcome measures of this study included the change in BCVA and CRT. Secondary outcome measure was the number of visits and injections.

Statistical analysis

Visual acuity was converted from decimals to the logarithm of the minimum angle of resolution (LogMAR) for statistical analysis. Categorical variables were presented as numbers and percentages, while numerical variables were expressed as the mean and standard deviation. First the data was analyzed in terms of normality using Shapiro-Wilk test. As the distribution of the data was found to be normal, the visual acuity and the CRT values between baseline and the other time points were assessed with repeated measures test. Categorical variables were compared using chi-square test. A p value < 0.05 was considered statistically significant.

Results

Forty-two eyes of 42 patients were included. Mean age was 60.7 ± 11.7 years (range 37–90). Fourteen of the patients (33.3%) had CRVO, and 28 (66.7%) had BRVO. Twenty-three patients (54.8%) were treatment naïve, whereas 19 (45.2%) had persistent ME. Persistent macular edema was defined as experiencing a partial or no response to any previous treatment options other than IVAfl. Mean follow-up time was 15.7 ± 3.3 months (range 12–22 months). Twenty of the

42 patients (47.6%) required panretinal or sectorial laser photocoagulation during the follow-up and none of the patients showed neovascular glaucoma. The baseline general characteristics were summarized in Table 1.

Mean BCVA at baseline and months 3, 6, 9, 12, at the last follow-up was 0.98 ± 0.58 LogMAR (range: 0.05–1.8), 0.84 ± 0.65 LogMAR (range: 0.1–3.0), 0.88 ± 0.70 , (range: 0.1–3.0), 0.82 ± 0.64 LogMAR (range: 0.0–3.0), 0.82 ± 0.65 LogMAR (range: 0.0–3.0) and 0.82 ± 0.69 LogMAR (range: 0.0–3.0), respectively (Fig. 1). With the exception of month 3, BCVA was statistically better at all time points than mean baseline ($p = 0.04$ for month 3, $p = 0.3$ for month 6, $p = 0.03$ for month 9, $p = 0.04$ for month 12, and $p = 0.04$ for the last follow-up). At month 12, 12 patients (28.6%) gained ≥ 3 lines of VA, 25 (59.5%) had a stable VA (< 3 lines of VA gain, stable, or < 3 lines of VA loss), and 5 (11.9%) lost ≥ 3 lines of VA. In CRVO subgroup, mean BCVA at baseline and months 3, 6, 9, 12, at the last follow-up was 1.20 ± 0.58 LogMAR (range: 0.20–1.8), 1.10 ± 0.65 LogMAR (range: 0.0–2.1), 1.05 ± 0.58 , (range: 0.1–1.8), 1.04 ± 0.61 LogMAR (range: 0.1–1.8), 1.06 ± 0.60 LogMAR (range: 0.1–1.8) and 1.11 ± 0.65 LogMAR (range: 0.0–1.8), respectively (Fig. 1) ($p > 0.05$ for all time points versus baseline). In BRVO subgroup, mean BCVA at baseline and months 3, 6, 9, 12, at the last follow-up subgroup was 0.87 ± 0.56 LogMAR (range: 0.05–1.8), 0.71 ± 0.62 LogMAR (range: 0.05–3.0), 0.80 ± 0.75 , (range: 0.1–3.0), 0.70 ± 0.63 LogMAR (range: 0.0–3.0), 0.70 ± 0.65 LogMAR (range: 0.0–3.0) and 0.67 ± 0.67 LogMAR (range: 0.0–3.0), respectively (Fig. 1). ($p > 0.05$ for all time points versus baseline).

Mean baseline CRT was 511 ± 141 μm (range: 240–859 μm). Mean CRT at months 3, 6, 9, 12, and at the last follow-up was 338 ± 141 μm (range: 186–786), 350 ± 153 μm (range: 204–733), 344 ± 132 μm (range: 196–670), 304 ± 95 μm (range: 196–594), and 343 ± 141 μm (range: 199–733), respectively (Fig. 2). Mean CRT level was statistically lower than mean baseline BCVA at all time points ($p < 0.0001$ for all). At month 12, 17 of the 45 patients (66.7%) had a CRT < 350 μm . In CRVO subgroup, mean baseline CRT was 545 ± 175 μm (range: 240–859 μm). Mean CRT at months 3, 6, 9, 12, and at the last follow-up was 334 ± 184 μm (range: 193–786), 266 ± 47 μm (range: 204–322), 321 ± 111 μm (range: 196–499), 309 ± 105 μm (range: 208–469), and 332 ± 157 μm (range: 205–662), respectively (Fig. 2). In BRVO subgroup, mean baseline CRT was 493 ± 119 μm (range: 293–697 μm). Mean CRT at months 3, 6, 9, 12, and at the last follow-up was 340 ± 116 μm (range: 186–550), 380 ± 167 μm

(range: 208–733), 353 ± 141 μm (range: 220–670), 303 ± 93 μm (range: 196–594), and 349 ± 137 μm (range: 196–733), respectively (Fig. 2).

Mean number of visits was 5.9 ± 2.1 (range 3–11) and injections was 3.2 ± 1.7 (range 1–8) at month 12. Twenty-two patients (52.4%) received 3 loading month loading doses IVAfl initially, whereas 20 patients (47.6%) did not receive. Seven patients (16.6%) required additional intravitreal dexamethasone injections during the follow-up.

No injection-related endophthalmitis was noted after total of 135 injections.

Discussion

In this study, we evaluated the real-life outcomes of IVAfl treatment for ME secondary to RVO. Baseline BCVA increased significantly from 0.98 to 0.82 LogMAR from baseline to month 12. The mean increase was noted as 1.6 LogMAR lines and 28.6% of the patients gained ≥ 3 lines of VA. Central retinal thickness was also significantly decreased from 511 to 304 μm at month 12 and 66.7% of the patients had a CRT < 350 . Mean number of visits and injections were 5.9 and 3.2 at month 12, respectively.

It is a known fact that the outcomes of prospective randomized clinical trials and real life practice studies are usually different in the treatment of retinal diseases with anti-VEGF agents.^{3,8–16} Several studies were conducted to evaluate this phenomenon.^{3,15,16} Ranibizumab was evaluated in the treatment of ME secondary CRVO and BRVO in two pivotal studies; CRUISE and BRAVO.^{8,9} In both of the studies patients were treated on an as-needed treatment regimen after 6 consecutive monthly injections. At 12 months, VA increased by 13.9 letters, CRT decreased by 462 μm with a mean of 8.8 injections in CRUISE study and VA increased by 18 letters, CRT decreased by 347 μm with a mean of 8.5 injections in BRAVO study.^{8,9} In a real life study from our clinic, the real life outcomes of treatment naïve patients with ME secondary to RVO was evaluated.³ After a follow-up period of 12 months VA was found to be increased from 0.85 LogMAR to 0.57 LogMAR and CRT was decreased from 581 μm to 359 μm with a mean of 4.5 visits and 3.5 injections. After the introduction of aflibercept, several prospective, randomized studies were conducted to evaluate its efficacy in the treatment of RVO.^{10–12} In the GALILEO study by Ogura et al., 18 month outcomes of aflibercept treatment in the treatment of ME secondary to CRVO was evaluated.¹⁰ The treatment regimen was designed as 6 initial monthly loading doses then as-needed treatment with monthly follow-up visits. The VA was reported to increase by 16.9 letters with a mean of 8.5 injections at month 12. Also 60.2% of the patients gained ≥ 15 letters at month 12. The change in mean CRT was -423 μm at month 12. Heier et al. conducted a parallel study to GALILEO, the COPERNICUS study which was another prospective randomized study evaluated the 2-year outcomes of aflibercept in the treatment of ME secondary to RVO.¹¹ The treatment regimen of the study was identical to GALILEO study. The change in VA was reported as +16.2 letters at month 12 and +13 letters at month 24. At month 12, 55.3% and at month 24, 49.1% of the patients gained ≥ 15 letters of VA. The mean reduction of CRT from baseline to month 12 and 24 was 413 and 390 μm , respectively. The mean number of injections at month 12 was 8.7 and month

Table 1. General characteristics of the patients.

Number of eyes	42
Age (years)	60.7 ± 11.7
Gender (male/female)	27/15
Hypertension (%)	29 (69.0%)
Diabetes (%)	8 (19.0%)
Hyperlipidemia (%)	5 (11.9%)
Fluorescein Angiography (non-ischemic/ischemic)	21/21
Type of RVO (BRVO/CRVO)	28/14
Previous treatment (naïve/persistent)	23/19
Baseline BCVA (LogMAR)	0.98 ± 0.58
Baseline CRT (μm)	511 ± 141

BCVA, best corrected visual acuity; BRVO, branch retinal vein occlusion; CRT, central retinal thickness; CRVO, central retinal vein occlusion; RVO, retinal vein occlusion, LogMAR, logarithm of the minimum angle of resolution.

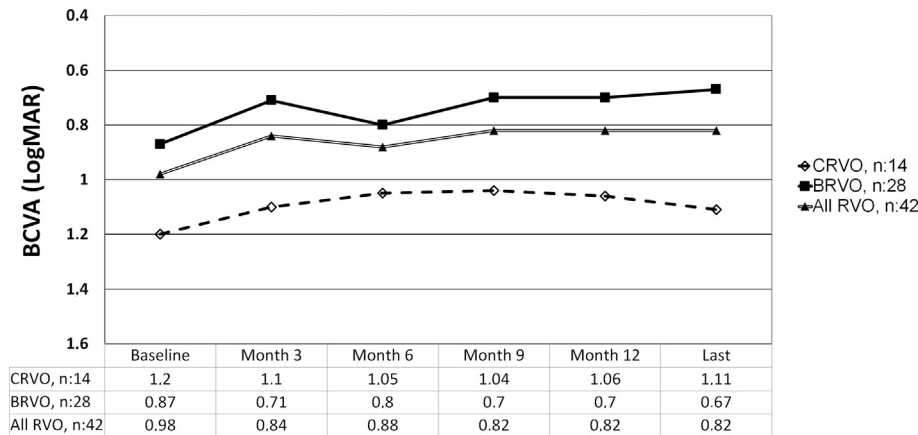


Fig. 1. The graph shows change in mean visual acuity levels from baseline to month 12. (CRVO, central retinal vein occlusion; BRVO, branch retinal vein occlusion; RVO, retinal vein occlusion; BCVA, best corrected visual acuity; LogMAR, logarithm of the minimum angle of resolution).

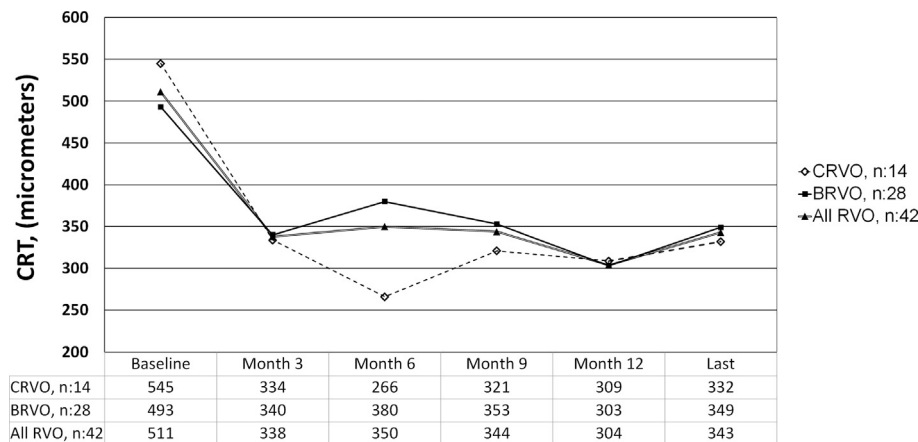


Fig. 2. The graph shows change in mean central retinal thickness from baseline to month 12. (CRVO, central retinal vein occlusion; BRVO, branch retinal vein occlusion; RVO, retinal vein occlusion; CRT, central retinal thickness).

14 was 12 injections. The efficacy of aflibercept in ME secondary to BRVO was evaluated in a prospective randomized trial- the VIBRANT study- by Clark et al.¹² The treatment regimen of this study was different from the other two CRVO studies. Patients first received 5 consecutive injections and then bimonthly fixed injections throughout 12 months. At month 12, patients received 9 injections, gained a mean of 17.1 letters and 57.1% of the patients gained ≥ 15 letters. The mean reduction in CRT from baseline to month 12 was 283 μm . The outcomes of aflibercept treatment in ME secondary to RVO were very successful. More than 50% of the patients showed ≥ 15 letters of VA improvement for the first time and both ischemic and non-ischemic subgroups were included in these three studies. Then a few real-life studies regarding the outcomes of aflibercept treatment patients with ME secondary to RVO were published.^{13,14} In a real-life study by Chatziralli et al., the outcomes of ranibizumab and aflibercept were compared in the treatment of ME secondary to CRVO.¹³ The aflibercept group of the study gained 8.3 and 7.5 letters at month 12 and 18 letters respectively. The mean baseline CRT decreased by 241 and 234 μm at month 12 and 18, respectively. At month 12 50% of the patients demonstrated complete resolution of ME. The mean injection number was reported as 6.1 at month 18. Our month 12 outcomes were similar with this study. The change in VA

was +1.6 LogMAR (approximately +8 letters) lines and CRT was $-207 \mu\text{m}$.

The main limitation of this study was the retrospective design. We evaluated the BRVO and CRVO patients together in a single study because of the low patient number. However, the study is a real-life study with relatively long follow-up period. There are a few studies in the literature regarding the outcomes of aflibercept treatment in ME secondary to RVO in real life. This study might contribute to the literature in this regard.

In conclusion, intravitreal aflibercept treatment seemed to be effective in patients with ME secondary to RVO with respect to visual and anatomical outcomes. In this study the number of visits and injections was lower than randomized controlled trials, but the functional and anatomical outcomes are probably still acceptable.

Conflict of interest

The authors declared that there is no conflict of interest.

Acknowledgements

The authors thank Dr. Hande Mefkure Ozkaya for review and language editing of the manuscript.

References

1. Scott IU, VanVeldhuisen PC, Oden NL, et al. SCORE Study Report 1: baseline association between central retinal thickness and visual acuity in patients with retinal vein occlusion. *Ophthalmology* 2009;**116**:504–12.
2. Yeh S, Kim SJ, Ho AC, Schoenberger SD, Bakri SJ, Ehlers JP, et al. Therapies for macular edema associated with central retinal vein occlusion: a report by the American Academy of Ophthalmology. *Ophthalmology* 2015;**122**:769–78.
3. Ozkaya A, Alkin Z, Yesilkaya C, et al. Ranibizumab in macular edema secondary to retinal vein occlusion in a real life practice: a retrospective case series. *Beyoglu Eye J* 2016;**1**:5–9.
4. The Branch Vein Study Group. Argon Laser photocoagulation for macular edema in branch vein occlusion. *Am J Ophthalmol* 1984;**98**:271–82.
5. Bhagat N, Goldberg MF, Gascon P, Bell W, Haberman J, Zarbin MA. Central retinal vein occlusion: review of management. *Eur J Ophthalmol* 1999;**9**:165–80.
6. Ozkaya A, Celik U, Alkin Z, et al. Comparison between intravitreal triamcinolone with grid laser photocoagulation versus bevacizumab with grid laser photocoagulation combinations for branch retinal vein occlusion. *ISRN Ophthalmol* 2013;**2013**:141279.
7. Korobelnik JF, Kodjikian L, Delcourt C, et al. Two-year, prospective, multicenter study of the use of dexamethasone intravitreal implant for treatment of macular edema secondary to retinal vein occlusion in the clinical setting in France. *Graefes Arch Clin Exp Ophthalmol* 2016;**254**:2307–18.
8. Brown DM, Campochiaro PA, Bhisitkul RB, et al. Sustained benefits from ranibizumab for macular edema following branch retinal vein occlusion: 12-month outcomes of a phase III study. *Ophthalmology* 2011;**118**:1594–602.
9. Brown DM, Campochiaro PA, Singh RP, et al. CRUISE investigators. Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study. *Ophthalmology* 2010;**117**:1124–33.
10. Ogura Y, Roider J, Korobelnik JF, et al. GALILEO study group. Intravitreal aflibercept for macular edema secondary to central retinal vein occlusion: 18-month results of the phase 3 GALILEO study. *Am J Ophthalmol* 2014;**158**:1032–8.
11. Heier JS, Clark WL, Boyer DS, Brown DM, Vitti R, Berliner AJ, et al. Intravitreal aflibercept injection for macular edema due to central retinal vein occlusion; two year results from the COPERNICUS study. *Ophthalmology* 2014;**121**:1414–20.
12. Clark WL, Boyer DS, Heier JS, et al. Intravitreal Aflibercept for Macular Edema Following Branch Retinal Vein Occlusion: 52-Week Results of the VIBRANT Study. *Ophthalmology* 2016;**123**:330–6.
13. Chatziralli I, Theodossiadis G, Moschos MM, Mitropoulos P, Theodossiadis P. Ranibizumab versus aflibercept for macular edema due to central retinal vein occlusion: 18-month results in real-life data. *Graefes Arch Clin Ophthalmol* 2017;**255**:1093–100.
14. Ozkaya A, Garip R, Yesilkaya C, Alkin Z, Taskapili M. Ranibizumab versus aflibercept in macular edema secondary to retinal vein occlusion in real life: a retrospective case control study. *Beyoglu Eye J* 2017;**2**:13–8.
15. Sakanishi Y, Lee A, Usui-Ouchi A, Ito R, Ebihara N. Twelve-month outcomes in patients with retinal vein occlusion treated with low-frequency intravitreal ranibizumab. *Clin Ophthalmol* 2016;**10**:1161–5.
16. Miwa Y, Muraoka Y, Osaka R, Ooto S, Murakami T, Suzuma K, et al. Ranibizumab for macular edema after branch retinal vein occlusion: one initial injection versus three monthly injections. *Retina* 2017;**37**:702–9.