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Original Article

Decreased reduction ratio of maximum retinal thickness after a second anti-VEGF injection

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Abstract: Anti-VEGF based medicines have revolutionized the treatment paradigm for patients with ocular neovascularization and preserved the vision in most of the patients; this has become the first line therapy in the treatment of choroidal neovascularization (CNV). The decreased efficacy for anti-VEGF reagents was reported after multiple injections in certain patients for unknown reason, however no literature has reported the change of efficacy of the anti-VEGF therapy at early stages. Due to lack of a sensitive parameter to evaluate the efficacy of anti-VEGF reagents in the treatment of CNV, we developed a new method in this study, i.e., the reduction ratio of the maximum retinal thickness (MRT), to evaluate its efficacy. A retrospective, non-randomized study was analyzed in 30 eyes of 29 patients with CNV. The patients were intravitreally injected with either ranibizumab (12 eyes) or conbercept (18 eyes) for 2 consecutive injections at a 1-month interval. Best-corrected visual acuity (BCVA) was measured. Optical coherence tomography angiography (OCTA) was used for the measurement of the MRT, central retinal thickness (CRT), vessel density before and after injections. The reduction ratio of MRT and CRT was calculated and compared. After intravitreal injection, the BCVA was improved; MRT, CRT as well as vessel density was decreased. The trend was maintained but with less effect after the second injection. When compared with the reduction ratio of MRT of the first injection, the reduction ratio of MRT of the second injection was decreased significantly in both ranibizumab- and conbercept-treated groups. In conclusion, the reduction ratio of MRT was decreased after the second intravitreal injection of anti-VEGF reagents. The reduction ratio of MRT might be a sensitive parameter to evaluate the efficacy of anti-VEGF reagents in the treatment of CNV.

Keywords: Choroidal neovascularization, anti-VEGF reagent, maximum retinal thickness, optical coherence tomography angiography

Introduction

Choroidal neovascularization (CNV), secondary to many ocular neovascular diseases such as wet age-related macular degeneration and pathologic myopia, is the pathological growth of new blood vessels from the choroid through a break in Bruch's membrane. CNV is one of the most important causes of visual impairment. At present, the main treatment for CNV treatment is intravitreal injection of anti-vascular endothelial growth factor (VEGF) reagents, such as ranibizumab, conbercept, aflibercept, etc. For most patients with CNV, anti-VEGF therapy was undoubtedly effective, but decreased efficacy was reported in a few patients after multiple injections, known as the "fast resistance" phenomenon [1-3]. However, no study explored the efficacy change of the anti-VEGF therapy, especially after the second injection.

The central retinal thickness (CRT) is a frequently used parameter to evaluate the effectiveness of anti-VEGF reagents on macular edema secondary to diabetic retinopathy and retinal vein occlusion [4-6], in which the absolute change of the retinal thickness was used. While, relative change of the retina, e.g., relative change in central retinal thickening (RCRTing) was used to evaluate the efficacy of anti-

Table 1. Patient general information and the improvement of BCVA

Parameters	Conbercept Group (n = 18)	Ranibizumab Group (n = 12)
Sex, No. (%)		
Male	9 (50)	8 (66.7)
Female	9 (50)	4 (33.3)
Age, mean (SD), y	69.4 (8.4)	67.5 (8.4)
BCVA, Mean (SD)		
Pre-injection	1.1 (0.5)	1.2 (0.7)
After 1st injection	0.9 (0.5)[a]	0.9 (0.5)[a]
After 2nd injection	1.0 (0.6)[b]	0.8 (0.5)

BCVA was expressed as LogMAR. [a]BCVA was significantly improved compared with pre-injection ($P < 0.05$). [b]The improvement (the difference between post-injection and pre-injection) of BCVA between the first injection and the second injection ($P < 0.05$).

VEGF reagents in the treatment of diabetic macular edema [7, 8] and macular edema secondary to retinal vein occlusion [9]. At present, no studies have reported using these parameters to evaluate the efficacy of anti-VEGF treatments for patients with CNV.

The parameter of RCRTing reflects the percentage of reduction in retinal thickness, which is subjective in evaluating the efficacy for the anti-VEGF treatment. However, the acquisition of the "normal retinal thickness" for the RCRTing calculation is difficult. In most studies [7-10], the average retinal thickness of a normal human retina from a database was used as the "normal retinal thickness", which does not reflect personalized variation. Furthermore, some severe retinal edema is not near the fovea in certain patients with CNV, and the central retinal thickness (CRT) might not be sensitive enough to reflect the severity of retinal edema compared to the maximum retinal thickness (MRT). Therefore, to find out a more sensitive method to evaluate the changes in retinal thickness before and after the treatments will be of great importance.

In the present study, a personalized MRT reduction ratio was used to study the changes in retinal thickness in patients with CNV after 2 consecutive intravitreal injections of anti-VEGF reagents. The data showed that both ranibizumab and conbercept are effective to treat CNV in terms of BCVA, vessel density, MRT as well as CRT after the first injection. However, the reduction ratio of MRT is decreased significantly after the second injection for both ranibizumab and conbercept, indicating the decreasing efficacy after a second anti-VEGF treatment.

Material and methods

General information

Twenty-nine patients with CNV were included, who underwent intravitreal injections of anti-VEGF reagents in the Wuhu Eye Hospital, in Wuhu, China from October 1, 2017 to October 31, 2018. Institutional ethics committee approval was obtained from the Wuhu Eye Hospital, and the study was performed according to the Declaration of Helsinki. All participants provided written informed consent. Inclusion criteria included: (1) CNV was confirmed with OCTA examination; (2) no history of anti-VEGF injection or other treatments such as photodynamic therapy in the past 6 months; (3) the interval between the first and the second injection was 1 month ± 1 week; and (4) all the parameters were collected, such as best corrected visual acuity (BCVA) and OCTA data, etc. The exclusion criteria were: (1) macular edema was secondary to other ocular diseases, e.g., diabetic retinopathy and retinal vein occlusion; (2) treatment for CNV was performed within 6 months; (3) incomplete data collection; and (4) images with low quality were obtained with OCTA, which prevented accurate analysis. Seventeen patients (9 males and 8 females, total 18 eyes) were injected intravitreally with conbercept (Chengdu Kanghong Biotechnologies Co. Ltd) with an average age of 69.4 ± 8.4 years (age range 53-89 years); 12 patients (8 males and 4 females, total 12 eyes) were injected with ranibizumab (Lucentis, Novartis Pharma Schweiz AG, Switzerland) with an average age of 67.5 ± 8.4 years (age range 51-83 years old) (**Table 1**).

Maximum retinal thickness (MRT) measurement

The maximum retinal thickness (MRT) was measured using OCTA (OPTOVUE RTVue XR Avanti System). MRT was measured three times and averaged before and after each injection. The same position was selected for MRT measurement in the follow-up based on the characteristic morphology of the retinal vessels. Three MRTs were collected, i.e., MRT1

(before injection), MRT2 (1 month after the first injection) and MRT3 (1 month after the second injection).

Relatively normal retinal thickness measurement

The relatively normal retina thickness (Mn) was measured at four points, i.e., superior, inferior, nasal and temporal sides at the proximity of the junction between the thickened and normal retina, and was averaged as the relatively normal value. In a few patients with diffuse edema we were unable to locate the exact measurement points as above before the first injection, which were measured at the selected points and measured at the same sites during follow-up.

Central retinal thickness (CRT) and normal thickness of the central retina

The central retinal thickness (CRT) [11] within 1- or 6-mm diameter was measured automatically with OCTA before and after each injection with a total of 3 measurements, i.e., CRT1 (before injection), CRT2 (1 month after the first injection) and CRT3 (1 month after the second injection).

As for the normal thickness of central retina (CRTn), considering measurements with different machines were slightly different [8, 10], we used OCTA built-in healthy human central retinal thickness as the normal thickness of the retina, i.e., CRTn was 255.2 μm (within 1-mm diameter) and 288.9 μm (within 6-mm diameter), respectively.

Vessel density measurement

The central retinal vessel density (CRVD) [12] was directly measured using OCTA, which was set as 18% (within 1-mm diameter) and 43.2% (within 6-mm diameter), separately [13].

Calculation of the reduction ratio of MRT, CRT and vessel density

The reduction ratio of MRT after the first injection was calculated as [(MRT2-MRT1)/(MRT1-Mn)] * 100%. The reduction ratio of MRT after the second injection was calculated as [(MRT3-MRT2)/(MRT2-Mn)] * 100%.

The same method was applied to the calculation of the reduction ratio of CRT and CRVD, i.e., the reduction ratio of CRT after the first or second injection was calculated as [(CRT2-CRT1)/(CRT1-CRTn)] * 100% or [(CRT3-CRT2)/(CRT2-CRTn)] * 100%. The reduction ratio of CRVD for the first or second injection was calculated as [(CRVD2-CRVD1)/(CRVD1-CRVDn)] * 100% or [(CRVD3-RVD2)/(CRVD2-CRVDn)] * 100%.

Statistical analysis

Statistical analysis was performed using SPSS statistical software (Version 22.0, IBM Corp). The Shapiro-Wilk test was used to evaluate the normality of measurements. The Levene test was used to evaluate the homogeneity of measurements. Paired variables before and after conbercept or ranibizumab injection were analyzed using the Wilcoxon signed rank test or paired sample t-test based on the normality and the homogeneity test. Unpaired variables between conbercept and ranibizumab injection were analyzed using two independent sample rank sum test or two independent samples t-test based on the normality and the homogeneity test [9]. All statistical tests were two-tailed. Test level was set $\alpha = 0.05$ for t-test and rank sum test, and $\alpha = 0.1$ for normality test and homogeneity test. The data were expressed as Mean (SD), a *p* value of 0.05 or less was considered statistically significant.

Results

Improvement of BCVA after intravitreal injection of anti-VEGF reagents

The BCVA of the patients was significantly improved after the first injection of conbercept or ranibizumab ($P < 0.05$). The BCVA was increased about 0.2 LogMAR ($Z = -2.409$, $P = 0.016$) for conbercept-treated group and 0.3 LogMAR ($Z = -2.825$, $P = 0.005$) for ranibizumab-treated group. After the second intravitreal injection, the visual acuity was further improved, but remained relatively low compared with that for the first injection. The difference of visual acuity between the second and the first injection was statistically significant ($Z = -2.115$, $P = 0.034$) for patients who received conbercept, but not ranibizumab (**Table 1**).

Reduction of superficial vessel density

One month after the first injection of both conbercept and ranibizumab, the superficial vessel density of the retina within 1-mm diameter was

Table 2. The absolute and relative change of CRVD within 1-mm diameter

Parameters	Conbercept Group (n = 16)	Ranibizumab Group (n = 11)
Pre-injection	25.8 (10.6)	25.0 (8.1)
After 1st injection	21.3 (10.9)[a]	21.5 (8.3)[a]
After 2nd injection	19.9 (9.9)	17.5 (6.4)
The reduction ratio of CRVD after the 1st injection	-2.1 (7.7)	/
The reduction ratio of CRVD after the 2nd injection	8.3 (35.1)	-0.8 (1.7)

The CRVD was expressed as Mean (SD). The normal vessel density was equal to 18%. The reduction ratio of CRVD (%) after the first injection of ranibizumab failed to be calculated due to a patient's pre-injection vessel density being 18%. [a]Vessel density was significantly decreased compared with pre-injection ($P < 0.05$).

Table 3. The absolute and relative change of MRT

Parameters	Conbercept Group (n = 18)	Ranibizumab Group (n = 12)
Pre-injection	634 (222)	603 (96)
After 1st injection	518 (162)[a]	470 (103)[a]
After 2nd injection	501 (160)[b]	437 (105)[b]
The reduction ratio of MRT after the 1st injection	-0.33 (0.23)	-0.44 (0.29)
The reduction ratio of MRT after the 2nd injection	-0.13 (0.25)[c]	-0.22 (0.18)[c]

The absolute change of MRT was expressed as mean (SD) (μm). [a]The MRT was significantly decreased compared with pre-injection ($P < 0.05$). [b]The MRT was significantly decreased compared with the first injection ($P < 0.05$). [c]The reduction ratio of MRT (%) was significantly decreased compared with the first injection ($P < 0.05$).

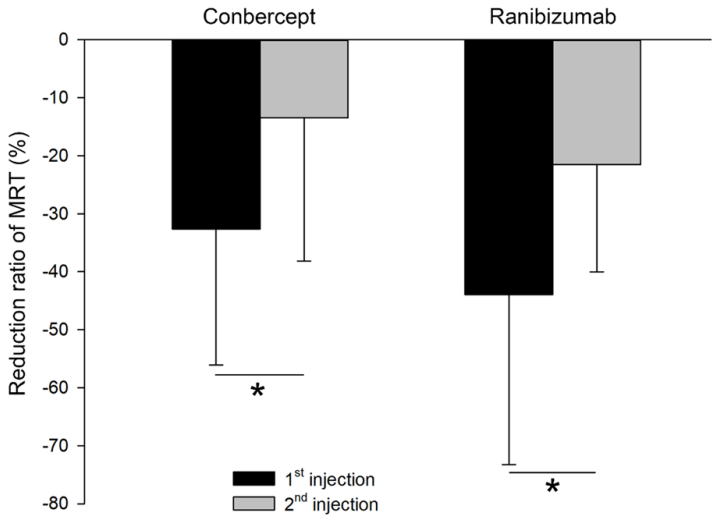

Figure 1. The reduction ratio of MRT in both conbercept and ranibizumab treated groups. *Means $P < 0.05$ between the first and second intravitreal injections, n = 18 in conbercept treated group and n = 12 in ranibizumab treated group.

significantly decreased. The vessel density was reduced by approximately 4.5% ($Z = -2.741$, $P = 0.006$) and 3.5% ($t = 2.328$, $P = 0.042$) for conbercept- and ranibizumab-treated groups, respectively. One month after the second injection, the superficial vessel density within 1-mm diameter was slightly lower than that after the first injection without statistical significance ($P > 0.05$). There was no significant difference between the two reduction ratios of CRVD for the conbercept-treated group. The first reduction ratio of CRVD for ranibizumab cannot be calculated due to the fact that the preoperative vessel density was 18%, leading to the denominator equaling 0 (**Table 2**). There was no statistical difference for the superficial vessel density within a 6-mm diameter.

Reduction of MRT after injections

In patients who received conbercept, the MRT was significantly decreased after the first injection compared with that before injection ($P < 0.05$). The MRT was decreased by 115 μm ($Z = -3.724$, $P < 0.001$, first injection) and 17 μm ($Z = -2.266$, $P = 0.023$, second injection), indicating conbercept was effective to decrease macular edema (**Table 3**; **Figure 1**). The reduction ratio of MRT was -33% after the first injection of conbercept, which was -13% after the second injection. The differ-

Table 4. The absolute and relative change of the CRT

Parameters	Conbercept Group (n = 16)	Ranibizumab Group (n = 11)
CRT (μm) or reduction ratio of CRT (%) within 6-mm diameter		
Pre-injection	316 (111)	307 (105)
After 1st injection	281 (98)[a]	266 (81)[a]
After 2nd injection	274 (75)[b]	260 (80)[c]
The reduction ratio of MRT after the 1st injection	-1.94 (7.04)	0.04 (2.69)
The reduction ratio of MRT after the 2nd injection	-1.16 (4.58)	-0.55 (1.22)
CRT (μm) or reduction ratio of CRT (%) within 1-mm diameter		
Pre-injection	400 (158)	404 (135)
After 1st injection	326 (138)	271 (72)[a]
After 2nd injection	322 (183)	261 (74)
The reduction ratio of MRT after the 1st injection	-0.96 (1.40)	-4.33 (11.03)
The reduction ratio of MRT after the 2nd injection	0.28 (4.18)	-0.91 (2.87)

The absolute change of the CRT was expressed as mean (SD) (μm). For the reduction ratio (%) of CRT (within 6-mm diameter), the normal CRT was equal to 288.9 μm; for the reduction ratio of CRT (within 1-mm diameter), the normal CRT was equal to 255.2 μm. Some patients were excluded because the CRT couldn't been normally displayed. [a]The CRT was significantly decreased compared with pre-injection ($P < 0.05$). [b]The CRT was significantly decreased compared with the first injection ($P < 0.05$). [c]The reduction (the difference between post-injection and pre-injection) of CRT between the first injection and the second injection ($P < 0.05$).

ence (about 20%) between the two injections was statistically significant ($Z = -3.018$, $P = 0.003$), indicating the efficacy was decreased for conbercept after the second injection in the treatment of CNV.

The same pattern was also found in patients treated with ranibizumab. The MRT was decreased by 133 μm ($t = 5.008$, $P < 0.001$) and 33 μm ($Z = -3.059$, $P = 0.002$) after the first and second injections (**Table 3**; **Figure 1**). The reduction ratio of MRT was -44% and -22% for the first and second injection of ranibizumab, separately. The difference for two reduction ratios of MRT was statistically significant ($t = -3.207$, $P = 0.008$), indicating that the efficacy of ranibizumab was also decreased after the second injection (**Table 3**; **Figure 1**). There was no significant difference for the reduction ratio of MRT between conbercept and ranibizumab treated groups.

Reduction of CRT after injections

The CRT was significant decreased in patients treated with conbercept or ranibizumab (**Table 4**). In patients who were injected with conbercept, the CRT within 6-mm diameter was decreased significantly after the injection (**Table 4**). The CRT was decreased by 35 μm ($Z = -3.054$, $P = 0.002$) after the first injection and 6 μm ($Z = -3.065$, $P = 0.002$) after the second injection. As for CRT within 1-mm diameter, the same trend was observed, but with no significant difference. The reduction ratio of CRT with 6-mm diameter was -194% after the first injection and -116% after the second injection. The reduction ratio of CRT with 1-mm diameter was -96% and 28% for the first and second injection, separately. However, no significant difference was found for the reduction ratio of CRT within 6-mm diameter or 1-mm diameter.

In patients who were injected with ranibizumab, the CRT within 6-mm diameter was decreased significantly after the injection (**Table 4**). The CRT was decreased about 41 μm ($Z = -2.936$, $P = 0.003$) after the first injection and 5 μm ($P > 0.05$) after the second injection. As for CRT within 1-mm diameter, the same trend was observed (**Table 4**). The reduction ratio of CRT with 6-mm diameter was 4% after the first injection and -55% after the second injection. The reduction ratio of CRT with 1-mm diameter was -433% and -91% for the first and second injection, separately. However, there is no significant difference for the reduction ratio of CRT within 6-mm diameter or 1-mm diameter.

Comparison of test efficiency

According to the present data, the minimum sample size estimation was calculated, and the minimum sample size was used to compare

the test efficiency. The minimum sample size for the calculation of the reduction ratio of MRT and CRT was calculated by using the online software: http://powerandsamplesize.com/Calculators/, using 1-Sample, 2-Sided Equality. The results showed that the minimum sample size required for the comparison of the reduction ratio of MRT before and after the injection of conbercept was 12 (the actual sample size in this study was 18).

The minimum sample requirement for the reduction ratio of CRT was 931 within 6-mm diameter and 99 within 1-mm diameter. Due to the requirement of large sample size for the calculation of the reduction ratio of CRT, the relatively small size in this study leads to inaccurate analysis. A similar trend was also tested in ranibizumab-treated group. The relatively small sample size was required for the calculation of the reduction ratio of MRT compared with CRT, indicating that the reduction ratio of MRT might be a sensitive method to evaluate the efficacy of anti-VEGF reagents.

Discussion

Anti-VEGF reagents, like bevacizumab, ranibizumab, aflibercept, and conbercept, have become a first line therapy in the treatment of neovascular diseases, such as CNV and proliferative diabetic retinopathy. To evaluate the efficacy of these anti-VEGF reagents in reducing retinal thickness, most previous studies used the absolute change of retinal thickness [11, 14, 15]. Although the absolute change of retinal thickness can be helpful in determinating the efficacy of anti-VEGF reagents, it might not be sensitive enough to evaluate the effect of anti-VEGF reagents after each treatment, i.e., the reduction ratio after each treatment. Thus, the reduction ratio of MRT or CRT might be an objective and sensitive method to reflect the efficacy after each treatment. In this study, we found that the reduction ratio of MRT, as a sensitive and repeatable parameter, could be used to evaluate the effectiveness of conbercept and ranibizumab for treatment of CNV.

This study demonstrated that the reduction ratio of MRT after the second injection of anti-VEGF reagents was significantly decreased over that after the first injection, indicating the efficacy was attenuated after the second treatment. This result was similar to the phenomenon of "fast resistance" in some patients who were unresponsive to anti-VEGF therapy [2, 16-20]. The possible reasons for this general "resistance" are as follows: the first injection of anti-VEGF reagents destroys most of the immature choroidal neovascularization or immature endothelial cells, leaving the relative large blood vessels that are less responsive or unresponsive to the second treatment [21-23]; antibodies against anti-VEGF reagents were produced after the first injection, thus binding and decreasing the effect of anti-VEGF reagents [24]; other factors besides VEGF might be also involved in the pathogenesis of CNV, such as inflammatory factors [25]. Previous studies reported that the efficacy will be regained in some patients who were less responsive to an anti-VEGF reagents when they were treated with increased doses or increased frequency of anti-VEGF reagents [26]. Since the present study was a retrospective study with a small sample size, the hypothesis needs to be validated with prospective or randomized controlled trials.

During the data procession, we found the reduction ratio of MRT could be used as a surrogate parameter and was sensitive enough to demonstrate the efficacy of anti-VEGF therapy instead of CRT. The possible reasons are the "normal CRT" is referred to as the normal input population built in the OCTA machine, which is not personalized [7-10], while the normal MRT used in the present study was based on personalized data to make the reduction ratio of the MRT is more accurate. In some patients, the value of CRT is very close to the reference data (CRTn) making the difference of CRT-CRTn nearly zero. As the denominator of this difference, the reduction ratio of CRT would vary largely [8, 10], thus decreasing the test efficiency. In some patients, the area of CNV is away from the fovea, using CRTn as the reference control will lead to a large variation in the reduction ratio. While MRTn was measured by selecting the 4 nearest points to reduce this variation largely. In addition, the CRT data cannot be displayed by OCTA causing missing data in some patients, e.g. in our conbercept-injected group, CRT and vessel density could not be obtained in 2 out of 18 eyes, reducing the sample size. To avoid this problem, we measured the MRT manually. So the reduction ratio of MRT might be a better method than the reduction ratio of CRT due to its small sample size and manual

measurement, which could be more sensitive in the evaluation of the efficacy of anti-VEGF therapy.

This study has shown that anti-VEGF therapy is effective in the treatment of CNV in terms of improved BCVA, decreased vessel density as well as the reduction of retinal edema. However, the reduction ratio of MRT was decreased after the second intravitreal injections for both conbercept and ranibizumab, indicating the efficacy of the second anti-VEGF therapy was attenuated. Compared with the reduction ratio of CRT, the reduction ratio of MRT might be a sensitive parameter to evaluate the effectiveness of anti-VEGF reagents in the treatments of CNV or other retinal neovascular diseases.

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Disclosure of conflict of interest

None.

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References

[1] Budzinskaya MV, Plyukhova AA and Sorokin PA. Anti-VEGF therapy resistance in neovascular age-related macular degeneration. Vestn Oftalmol 2017; 133: 103-108.

[2] Gasperini JL, Fawzi AA, Khondkaryan A, Lam L, Chong LP, Eliott D, Walsh AC, Hwang J and Sadda SR. Bevacizumab and ranibizumab tachyphylaxis in the treatment of choroidal neovascularisation. Br J Ophthalmol 2012; 96: 14-20.

[3] Yang S, Zhao J and Sun X. Resistance to anti-VEGF therapy in neovascular age-related macular degeneration: a comprehensive review. Drug Des Devel Ther 2016; 10: 1857-1867.

[4] Kulikov AN, Sosnovskii SV, Berezin RD, Maltsev DS, Oskanov DH and Gribanov NA. Vitreoretinal interface abnormalities in diabetic macular edema and effectiveness of anti-VEGF therapy: an optical coherence tomography study. Clin Ophthalmol 2017; 11: 1995-2002.

[5] Ozkaya A, Tulu B and Garip R. Aflibercept in macular edema secondary to retinal vein occlusion: a real life study. Saudi J Ophthalmol 2017; 31: 211-215.

[6] Shah AR, Yonekawa Y, Todorich B, Van Laere L, Hussain R, Woodward MA, Abbey AM and Wolfe JD. Prediction of anti-VEGF response in diabetic macular edema after 1 injection. J Vitreoretin Dis 2017; 1: 169-174.

[7] Browning DJ, Glassman AR, Aiello LP, Bressler NM, Bressler SB, Danis RP, Davis MD, Ferris FL, Huang SS, Kaiser PK, Kollman C, Sadda S, Scott IU and Qin H; Diabetic Retinopathy Clinical Research Network. Optical coherence tomography measurements and analysis methods in optical coherence tomography studies of diabetic macular edema. Ophthalmology 2008; 115: 1366-1371.

[8] Chan A and Duker JS. A standardized method for reporting changes in macular thickening using optical coherence tomography. Arch Ophthalmol 2005; 123: 939-943.

[9] Gokce G, Sobaci G, Durukan AH and Erdurman FC. The comparison of intravitreal triamcinolone and bevacizumab in patients with macular edema secondary to branch retinal vein occlusion. Clin Ophthalmol 2014; 8: 355-362.

[10] Mitkova-Hristova VT and Konareva-Kostyaneva MI. Macular thickness measurements in healthy eyes using spectral optical coherence tomography. Folia Medica (Plovdiv) 2011; 53: 28-33.

[11] Li X, Wang N, Liang X, Xu G, Li XY, Jiao J, Lou J and Hashad Y; China Ozurdex in RVO Study Group. Safety and efficacy of dexamethasone intravitreal implant for treatment of macular edema secondary to retinal vein occlusion in Chinese patients: randomized, sham-controlled, multicenter study. Graefes Arch Clin Exp Ophthalmol 2018; 256: 59-69.

[12] Lee MW, Kim KM, Lim HB, Jo YJ and Kim JY. Repeatability of vessel density measurements using optical coherence tomography angiography in retinal diseases. Br J Ophthalmol 2018; [Epub ahead of print].

[13] Chen HS, Liu CH, Wu WC, Tseng HJ and Lee YS. Optical coherence tomography angiography of

the superficial microvasculature in the macular and peripapillary areas in glaucomatous and healthy eyes. Invest Ophthalmol Vis Sci 2017; 58: 3637-3645.
[14] Mathews NR, Tarima S, Kim DG and Kim JE. Foveal contour changes following surgery for idiopathic epiretinal membrane. Invest Ophthalmol Vis Sci 2014; 55: 7754-7760.
[15] Wiley HE, Thompson DJ, Bailey C, Chew EY, Cukras CA, Jaffe GJ, Lee RW, Loken EK, Meyerle CB, Wong W and Ferris FL 3rd. A crossover design for comparative efficacy: a 36-week randomized trial of bevacizumab and ranibizumab for diabetic macular edema. Ophthalmology 2016; 123: 841-849.
[16] Eghoj MS and Sorensen TL. Tachyphylaxis during treatment of exudative age-related macular degeneration with ranibizumab. Br J Ophthalmol 2012; 96: 21-23.
[17] Forooghian F, Cukras C, Meyerle CB, Chew EY and Wong WT. Tachyphylaxis after intravitreal bevacizumab for exudative age-related macular degeneration. Retina 2009; 29: 723-731.
[18] Gokce G, Durukan AH, Koylu MT and Kucukevcilioglu M. Efficacy of aflibercept on exudative age-related macular degeneration in patients exhibiting complete ranibizumab resistance and tachyphylaxis. Arq Bras Oftalmol 2016; 79: 384-389.
[19] Keane PA, Liakopoulos S, Ongchin SC, Heussen FM, Msutta S, Chang KT, Walsh AC and Sadda SR. Quantitative subanalysis of optical coherence tomography after treatment with ranibizumab for neovascular age-related macular degeneration. Invest Ophthalmol Vis Sci 2008; 49: 3115-3120.
[20] Schaal S, Kaplan HJ and Tezel TH. Is there tachyphylaxis to intravitreal anti-vascular endothelial growth factor pharmacotherapy in age-related macular degeneration? Ophthalmology 2008; 115: 2199-2205.
[21] Dansingani KK, Balaratnasingam C, Klufas MA, Sarraf D and Freund KB. Optical coherence tomography angiography of shallow irregular pigment epithelial detachments in pachychoroid spectrum disease. Am J Ophthalmol 2015; 160: 1243-1254.
[22] Dansingani KK and Freund KB. Optical coherence tomography angiography reveals mature, tangled vascular networks in eyes with neovascular age-related macular degeneration showing resistance to geographic atrophy. Ophthalmic Surg Lasers Imaging Retina 2015; 46: 907-912.
[23] El Ameen A, Cohen SY, Semoun O, Miere A, Srour M, Quaranta-El Maftouhi M, Oubraham H, Blanco-Garavito R, Querques G and Souied EH. Type 2 neovascularization secondary to age-related macular degeneration imaged by optical coherence tomography angiography. Retina 2015; 35: 2212-2218.
[24] Leveziel N, Pelat T, Watier H, Thullier P and Souied EH. Detection of antiranibizumab antibodies among patients with exudative age-related macular degeneration. Ophthalmologica 2014; 232: 53-56.
[25] Murugeswari P, Subramani M, Jayadev C, Shetty R and Das D. Retinal pigment epithelium-secretome: a diabetic retinopathy perspective. Cytokine 2017; 95: 126-135.
[26] You QS, Gaber R, Meshi A, Ramkumar HL, Alam M, Muftuoglu IK and Freeman WR. High-dose high-frequency aflibercept for recalcitrant neovascular age-related macular degeneration. Retina 2018; 38: 1156-1165.