ORIGINAL RESEARCH

Effectiveness Differences of Ranibizumab and Aflibercept Action in the Treatment of Diabetic Retinopathy

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ABSTRACT

Objective • To compare the difference in the effectiveness of ranibizumab (LU) and aflibercept (AF) in the treatment of diabetic retinopathy (DR).

Methods • Ninety-four patients with DR admitted to Sunshine Union Hospital from August 2020 to February 2022 were selected for the study and were divided into LU group (n = 47) and AF group (n = 47) according to the random number table method. Both groups underwent 25G vitrectomy in our hospital, with LU injected into the vitreous before surgery in the LU group and AF in the AF group. Vascular endothelial growth factor (VEGF) and pigment epithelium-derived factor (PEDF) in the pre-and post-injection atrial water were compared between the two groups, and the operative time, intraoperative bleeding, and the occurrence of medically induced fissures were recorded in both groups. In addition, the expression of best corrected visual acuity (BCVA), Central Macular Thickness (CMT), and inflammatory factors were compared before and after surgery. Finally, patients were counted for adverse reactions and prognosis of DR recurrence during treatment.

Results • After injection, VEGF decreased and PEDF increased in both groups ($P < .001$). There were no differences in operative time ($P = .604$), intraoperative bleeding rate ($P = .694$), the incidence of medically induced fissure ($P = .557$), BCVA [$P = .665$ (T0), $P > .999$ (T1), $P = .727$ (T2)], and CMT [$P = .688$ (T0), $P = .065$ (T1), $P = .148$ (T2)] between the two groups, while IL-6, IL-8, and MMP-9 were lower in the AF group than in the LU group at 2 months after surgery ($P < .001$). Finally, there was no difference between both groups in terms of adverse effects and prognosis of DR recurrence rate ($P = 1.000, .478$).

Conclusion • Both vitreous cavity injections of LU and AF can effectively reduce the expression of vascular-related factors in the atrial fluid of DR patients, but AF has a more significant inhibitory effect on the level of inflammatory factors in patients in the short term after treatment. (*Altern Ther Health Med.* 2024;30(1):441-445).

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INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease characterized by a chronic increase in blood glucose levels and is the most common type of chronic disease worldwide.[1] The prevalence of DM is climbing sharply as people's living standards improve.[2] According to statistics, more than 300 million cases of DM have been accumulated worldwide, and the proportion of patients under 40 years old is increasing, which shows that the onset of DM also shows a trend of gradual rejuvenation.[3] DM itself is not directly harmful, but in the long-term hyperglycemia can prompt a series of malignant lesions and adverse damage in the organism of patients, causing different degrees of organ function abnormalities, which can even threaten their lives in serious cases.[4] Among them, diabetic retinopathy (DR) is one of its most common and serious complications and is currently one of the main factors leading to acquired blindness in patients. The incidence of DR is closely related to the duration of DM. It is estimated that the incidence of DR is 25% at 5 years of DM, increases to 60% at 10 years of DM, and reaches 75-90% after 15 years of DM.[5]

Currently, 25G vitrectomy is one of the most prominent procedures for the treatment of DR, with the advantages of good results and small incisions.[6] However, DR patients are commonly associated with vitreous hemorrhage, which can increase the difficulty of 25G vitrectomy and affect the treatment outcome.[7] It has been found that vascular endothelial growth factor (VEGF) is a major cause of DM retinopathy and has an important role in retinal

neovascularization and in reducing vascular leakage.[8] Therefore, the success rate of 25G vitrectomy can be effectively enhanced by anti-VEGF drugs.[9] Clinically, both ranibizumab (LU) and aflibercept (AF) are drugs used to inhibit VEGF and improve symptoms such as blurred vision due to vascular growth and exudation,[10,11] but few studies have been conducted to compare the difference in the effectiveness of their use in 25G vitrectomy.

Clinically, both ranibizumab (LU) and aflibercept (AF) are drugs used to inhibit VEGF and improve symptoms such as blurred vision due to vascular growth and exudation,[10,11] but few studies have been conducted to compare the difference in the effectiveness of their use in 25G vitrectomy. By comparing the effect of LU and AF in DR surgery in this study, we can provide more reliable reference opinion and guidance for the future treatment of DR.

SUBJECTS AND METHODS

Patient data

Ninety-four patients with DR admitted from August 2020 to February 2022 were selected for the study with the approval of the Sunshine Union Hospital ethics committee. They were divided into the LU group (n = 47) and the AF group (n = 47) according to the random number table method. All study subjects signed an informed consent form by themselves.

Inclusion and exclusion criteria

Inclusion criteria: diagnosis of DR confirmed by fundus fluorescence angiography and other tests[12]; monocular lesions; vision loss with fundus manifestations; the presence of indications for vitrectomy; treated with anti-VEGF injections at our institution.

Exclusion criteria: patients with uncontrolled glaucoma, cataract, and previous treatment with intraocular injections or ophthalmic surgery; patients with combined malignancy and systemic diseases; patients with incomplete clinical data.

Methods

All patients improved metabolic index examination and fundus examination in Sunshine Union Hospital, defined surgical indications and indications. Seven days before the operation, antibiotics were given eye drops, ocular surface anesthesia, needle injection at 3.5mm behind corneal limbus, injection of anti-VEGF drugs, rapid needle out, cotton swab compression to stop bleeding, application of ofloxacin eye ointment and bandaging eyes. The LU group was given LU (Nosodexide Ranibizumab Injection, S20170003, Novartis Pharma Stein AG, Switzerland) 0.05 mL and the AF group was given AF (Eylea Abciximab Intraocular Solution, S20180001, Vetter Pharma-Fertigung GmbH & Co. KG, Germany) 0.05 mL, and vitrectomy was performed after no abnormalities. The surgeries were all performed by the same surgical team in Sunshine Union Hospital.

Table 1. Comparison of general data

	Age	Course of DM	Sex		Diseased eyes		Family history of the disease	
			Male	Female	Left Eye	Right Eye	Yes	No
LU group (n = 47)	57.13±5.72	6.66±2.17	29(61.70)	18(38.38)	22(46.81)	25(53.19)	8(17.02)	39(82.98)
AF Group (n = 47)	58.15±4.09	6.19±2.32	33(70.21)	14(29.79)	25(53.19)	22(46.81)	5(10.64)	42(89.36)
t or χ^2	0.994	1.014	0.758		0.383		0.734	
P value	323	0.313	.384		.536		.857	

Prognostic follow-up

Patients in both groups were followed up prognostically for 6 months, and the follow-up was performed in the form of regular hospital recurrences. The patients' prognosis of DR recurrence was recorded.

Outcome measures

(1) Before and after vitreous cavity injection, respectively, 0.1 mL of atrial fluid was collected by puncturing into the corneal rim, and the levels of VEGF and pigment epithelium-derived factor (PEDF) were detected by enzyme-linked immunosorbent assay (ELISA). (2) The operative time and intraoperative bleeding were recorded in both groups, and the occurrence of medically induced fissures was observed. (3) Patients were followed up at preoperative (T0), 2 months (T1), and 6 months (T2), respectively, and their best corrected visual acuity (BCVA) was examined by visual acuity chart, Central Macular Thickness (CMT) was measured by optical coherence tomography and fasting venous blood was collected for the detection of inflammatory factors interleukin 6 (IL-6), interleukin 6 (IL-8) and matrix metalloprotein-9 (MMP-9) by ELISA. The ELISA was performed to detect the inflammatory factors interleukin 6 (IL-6), interleukin 6 (IL-8), and matrix metalloprotein-9 (MMP-9). The kits were purchased from Beijing QuanShiJin Biotechnology Co., Ltd (China), and the operation was carried out in strict accordance with the instructions of the kits. (4) The incidence of adverse reactions during treatment, such as retinal detachment, transient eye pressure, etc., was counted. (5) Patients with DR recurrence at prognostic follow-up.

Statistical analysis

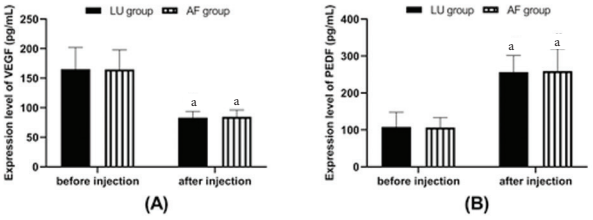
All statistical analyses in this study were done using Statistical Package for the Social Sciences (SPSS) version 21.0 software. The counting data were expressed in (%) and compared by the χ^2 tests. The measurement data were represented as ($\bar{x} \pm s$), and the t test was used for comparison between groups. Analysis of Variance (ANOVA) and Bonferroni intra-group test were for that between multiple groups. The difference was considered statistically remarkable at $P < .05$.

RESULTS

Comparison of general data

To ensure the reliability of the experimental results, we first conducted a preliminary comparison of the clinical baseline data of the two groups. The experimental results showed that no

Figure 1. Comparison of VEGF and PEDF. (A) VEGF. (B) PEDF. compared with before injection.



[a]$P < .05$

statistically significant differences were seen between the LU and AF groups in terms of age and gender ($P > .05$. Table 1).

Comparison of VEGF and PEDF

Before and after injection, the differences in VEGF and PEDF levels between the two groups were not statistically obvious ($P > .05$). After injection, VEGF decreased to (83.32±10.24) pg/mL and PEDF increased to (256.54±45.04) pg/mL in the LU group. VEGF decreased to (84.77±11.45) pg/mL and PEDF increased to (259.23±60.75) pg/mL after injection in the AF group (Figure 1).

Comparison of surgical situations

The operative times of the LU and AF groups were (25.94±5.14) min and (25.36±5.66) min, respectively, and the difference between the two groups was seen to be statistically insignificant ($P > .05$). Besides, the difference in the ratio of intraoperative bleeding rate and the incidence of medically induced fissure between both groups was likewise not statistically significant ($P > .05$, Table 2).

Comparison of treatment conditions

The differences in BCVA and CMT comparisons between the two groups at T0-T2 were likewise not statistically obvious ($P > .05$), and both BCVA and CMT decreased in both groups at T1 compared with T0. No change in BCVA was found in the LU and AF groups at T2 compared with T1, while CMT decreased further in both groups compared with T1 ($P < .05$, Figure 2).

Comparison of inflammation

The results of the comparison of the levels of inflammatory factors between groups showed no statistically marked differences at T0 and T2 ($P > .05$). While at T1, IL-6, IL-8, and MMP-9 were (69.16±5.79) pg/mL, (12.39±2.88) pg/mL, and (33.07±4.74) pg/mL, respectively, in the AF group, even lower than in the LU group ($P < .05$, Figure 3).

Comparison of adverse reactions

The incidence of adverse reactions was 4.26% in the LU group and 4.26% in the AF group. The difference in the incidence of adverse reactions between the two groups was not statistically obvious ($P > .05$, Table 3).

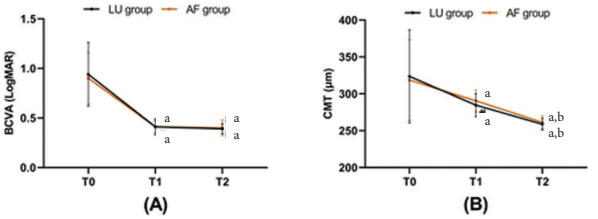
Comparison of prognosis

Forty-five cases in the LU group and 44 in the AF group

Table 2. Comparison of surgical situations

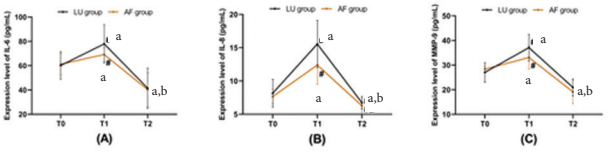
	Operation time (min)	Intraoperative bleeding	Medically induced fissures
LU group (n = 47)	25.94±5.14	3(6.38)	2(4.26)
AF Group (n = 47)	25.36±5.66	4(8.51)	1(2.13)
χ^2	0.520	0.154	0.344
P value	.604	.694	.557

Figure 2. Comparison of treatment conditions. (A) BCVA. (B) CMT. compared with T0



[a]$P < .05$. compared with T1
[b]$P < .05$

Figure 3. Comparison of inflammation. (A) IL-6. (B) IL-8. (C) MMP-9. compared with T0

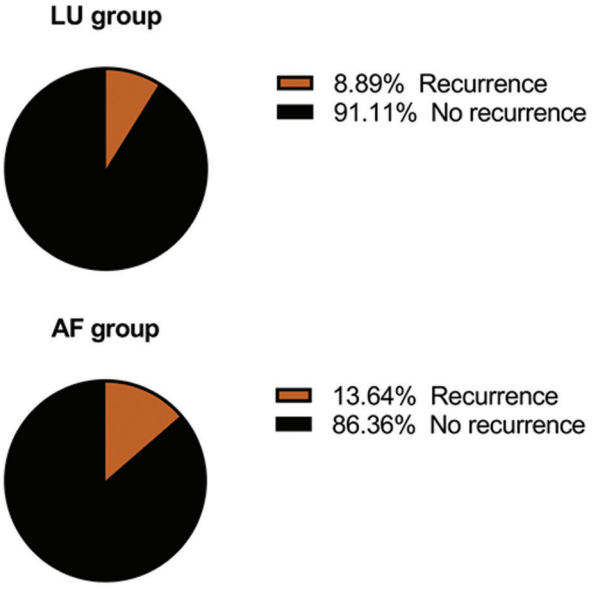


[a]$P < .05$ compared with T1
[b]$P < .05$ compared with the AF group

Table 3. Comparison of adverse reactions

	Retinal detachment	Transient high intraocular pressure	Vitreous hemorrhage	Total incidence
LU group (n = 47)	1(2.13)	0(0.0)	1(2.13)	4.26%
AF Group (n = 47)	0(0.0)	1(2.13)	1(2.13)	4.26%
χ^2				1.000
P value				1.000

Figure 4. Comparison of prognosis.



were successfully followed up in the prognostic follow-up. Four patients in the LU group had a recurrence of DR, with an overall recurrence rate of 8.89%. The overall recurrence rate of prognostic DR in the AF group was 13.64%. There was no statistically significant difference in the recurrence rate between the two groups ($P > .05$, Figure 4).

DISCUSSION

In the present study, we found that both LU and AF injections had a high safety profile in 25G vitrectomy for DR, but AF appeared to have a more significant inhibitory effect on the inflammatory response.

Patients with DR have fibrovascular membrane adhesions to the retina and commonly exhibit retinal edema and blood accumulation, which are highly susceptible to adverse events such as medically induced fissures and hemorrhage in the case of surgical forced detachment, which can have a significant negative impact on treatment.[13] Currently, neovascularization has been clinically identified as the main pathological basis for the development of DR and an important factor affecting the outcome of the procedure.[14] VEGF is a marker of neovascularization, and studies have demonstrated that inhibiting VEGF levels is sufficient to inhibit neovascularization.[15] Although there are clinical studies on the therapeutic effects of anti-VEGF drugs on DR, comparisons between the advantages and disadvantages of the drugs are still rarely reported. In the current study, we found no statistically significant differences in VEGF and PEDF levels between DR patients using LU and AF after injection, indicating that both drugs can effectively inhibit VEGF. At the same time, no differences were seen in the operative time, intraoperative bleeding rate, and medically induced fissure between the two groups, and the postoperative BCVA and CMT were likewise more consistent, which also suggests that both our LU and AF have a stable positive impact on DR surgery and can effectively contribute to the success of DR surgery. This is also consistent with the results of previous studies,[16,17] which can corroborate the results of the current experiment. It is well known that LU, approved for clinical treatment in 2006, is a fully-humanized monoclonal antibody fragment that binds non-specifically to the VEGF-A isoform and inhibits its binding to the receptor, thereby reducing neovascularization and edema [18]. Studies have shown that LU removes the Fc segment of the antibody molecule and therefore has better retinal penetration, and most of the drug can reach the retina after injection, with high efficiency of systemic clearance.[19] The main mechanism of AF, as a humanized VEGF receptor fusion protein, is to competitively bind VEGF and prevent VEGF receptor activation to exert its inhibitory effect on VEGF.[20] In previous studies, it was found that the use of AF had a stronger anti-VEGF effect with a significantly longer half-life in vascular macular endothelial disease.[21] It has also been found that both LU and AF are effective in improving visual acuity and macular morphology in patients with age-related macular degeneration.[22] In the present study, we saw no significant difference in the inhibitory effect of the two drugs on VEGF, presumably because the present study was mainly focused on the effect of LU and AF combined with vitrectomy for DR, and the duration of the two drugs was short, so the difference between the two groups was not marked. In the comparison of inflammatory factors, we saw that the levels of IL-6, IL-8, and MMP-9 were lower in the AF group at T1 than in the LU group, suggesting that we had a superior inhibitory effect of AF on the inflammation of patients in the short term of injection. It is well known that IL-6, IL-8 and MMP-9, as representative pro-inflammatory chemokines in the human body, are inflammatory chemotactic mediators produced by the human body under stressful conditions, and retinal microvascular ischemia and hypoxic injury in DM patients due to hyperglycemia will stimulate glial cells to secrete IL-6, IL-8 and MMP-9, prompting the loosening of connections between epithelial cells and vascular endothelial cells and boosting the production of proliferative and neovascular membranes in the eye.[23] Although the continued elevated levels of inflammatory factors can be effectively suppressed after the use of VEGF inhibitors, a series of operations such as anterior chamber puncture and surgical resection may all further contribute to a further elevation of the inflammation, followed by a gradual decrease as retinal function heals [24]. Because AF has a longer half-life in humans, it has a longer duration of action in the short term and can exert a longer VEGF inhibitory effect, so the inflammatory factor levels in patients in the AF group are slightly lower than those in the LU group in the short term. Finally, in the comparison of the adverse reactions and prognosis of the two groups, there was no difference in the adverse reactions and prognosis of recurrence, which indicates that both LU and AF have a high safety profile and have a stable effect on the prevention of disease recurrence after DR treatment, which also suggests that LU and AF have the potential to become DR preventive drugs in the future, but their optimal doses still need to be confirmed by further studies.

Nevertheless, due to the small number of cases included in this study, the possibility of statistical calculation chance cannot be excluded. Meanwhile, the significant difference between the two groups of patients may also be related to the duration and dose of the drug, so the choice of the dose used for LU versus AF is still the focus of an in-depth analysis. Finally, we also need to conduct in vitro experiments as soon as possible to confirm the specific mechanism of action of both drugs on DR.

CONCLUSION

Both vitreous cavity injection of LU and AF can effectively reduce the expression of vascular-related factors in the atrial fluid of DR patients and enhance the outcome of the procedure. There is a more consistent safety profile between the two, but AF has a more significant inhibitory effect on the level of inflammatory factors in patients in the short term after treatment. It is presumed that AF is preferred for future interventions when performing vitrectomy for DR.

REFERENCES

1. Harreiter J, Roden M. [Diabetes mellitus-Definition, classification, diagnosis, screening and prevention (Update 2019)]. *Wien Klin Wochenschr*. 2019;131(S1)(suppl 1):6-15. doi:10.1007/s00508-019-1450-4
2. Cole JB, Florez JC. Genetics of diabetes mellitus and diabetes complications. *Nat Rev Nephrol*. 2020;16(7):377-390. doi:10.1038/s41581-020-0278-5
3. Lovic D, Piperidou A, Zografou I, Grassos H, Pittaras A, Manolis A. The Growing Epidemic of Diabetes Mellitus. *Curr Vasc Pharmacol*. 2019;17(2). doi:10.2174/1570161117666190405165911
4. Petersmann A, Müller-Wieland D, Müller UA, et al. Definition, Classification, and Diagnosis of Diabetes Mellitus. *Experimental and Clinical Endocrinology & Diabetes*. 2019;127(S 01):S1-S7. doi:10.1055/a-1018-9078
5. Vujosevic S, Aldington SJ, Silva P, et al. Screening for diabetic retinopathy: new perspectives and challenges. *Lancet Diabetes Endocrinol*. 2020;8(4):337-347. doi:10.1016/S2213-8587(19)30411-5
6. Ding C, Wang N, Wang Z, et al. Integrated Analysis of Metabolomics and Lipidomics in Plasma of T2DM Patients with Diabetic Retinopathy. *Pharmaceutics*. 2022;14(12):2751-2751. doi:10.3390/pharmaceutics14122751
7. Simó-Servat O, Hernández C, Simó R. Diabetic Retinopathy in the Context of Patients with Diabetes. *Ophthalmic Res*. 2019;62(4):211-217. doi:10.1159/000499541
8. Tan Y, Fukutomi A, Sun MT, Durkin S, Gilhotra J, Chan WO. Anti-VEGF crunch syndrome in proliferative diabetic retinopathy: A review. *Surv Ophthalmol*. 2021;66(6):926-932. doi:10.1016/j.survophthal.2021.03.001
9. Yang Y, Liu Y, Li Y, et al. MicroRNA-15b Targets VEGF and Inhibits Angiogenesis in Proliferative Diabetic Retinopathy. *J Clin Endocrinol Metab*. 2020;105(11):3404-3415. doi:10.1210/clinem/dgaa538
10. Gross JG, Glassman AR, Liu D, et al; Diabetic Retinopathy Clinical Research Network. Five-Year Outcomes of Panretinal Photocoagulation vs Intravitreous Ranibizumab for Proliferative Diabetic Retinopathy: A Randomized Clinical Trial. *JAMA Ophthalmol*. 2018;136(10):1138-1148. doi:10.1001/jamaophthalmol.2018.3255
11. Brown DM, Wykoff CC, Boyer D, et al. Evaluation of Intravitreal Aflibercept for the Treatment of Severe Nonproliferative Diabetic Retinopathy: Results From the PANORAMA Randomized Clinical Trial. *JAMA Ophthalmol*. 2021;139(9):946-955. doi:10.1001/jamaophthalmol.2021.2809
12. Sabanayagam C, Banu R, Chee ML, et al. Incidence and progression of diabetic retinopathy: a systematic review. *Lancet Diabetes Endocrinol*. 2019;7(2):140-149. doi:10.1016/S2213-8587(18)30128-1
13. Li Y, Mitchell W, Elze T, Zebardast N. Association Between Diabetes, Diabetic Retinopathy, and Glaucoma. *Curr Diab Rep*. 2021;21(10):38. doi:10.1007/s11892-021-01404-5
14. Wong TY, Cheung CMG, Larsen M, Sharma S, Simó R. Diabetic retinopathy. *Nat Rev Dis Primers*. 2016;2(1):16012. doi:10.1038/nrdp.2016.12
15. Zhang D, Lv FL, Wang GH. Effects of HIF-1α on diabetic retinopathy angiogenesis and VEGF expression. *Eur Rev Med Pharmacol Sci*. 2018;22(16):5071-5076. doi:10.26355/eurrev_201808_15699
16. Sun JK, Glassman AR, Beaulieu WT, et al; Diabetic Retinopathy Clinical Research Network. Rationale and Application of the Protocol S Anti-Vascular Endothelial Growth Factor Algorithm for Proliferative Diabetic Retinopathy. *Ophthalmology*. 2019;126(1):87-95. doi:10.1016/j.ophtha.2018.08.001
17. Antoszyk AN, Glassman AR, Beaulieu WT, et al; DRCR Retina Network. Effect of Intravitreous Aflibercept vs Vitrectomy With Panretinal Photocoagulation on Visual Acuity in Patients With Vitreous Hemorrhage From Proliferative Diabetic Retinopathy: A Randomized Clinical Trial. *JAMA*. 2020;324(23):2383-2395. doi:10.1001/jama.2020.23027
18. Wells JA, Glassman AR, Ayala AR, et al; Diabetic Retinopathy Clinical Research Network. Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema: Two-Year Results from a Comparative Effectiveness Randomized Clinical Trial. *Ophthalmology*. 2016;123(6):1351-1359. doi:10.1016/j.ophtha.2016.02.022
19. Chatziralli I. Ranibizumab for the treatment of diabetic retinopathy. *Expert Opin Biol Ther*. 2021;21(8):991-997. doi:10.1080/14712598.2021.1928629
20. Wells JA, Glassman AR, Ayala AR, et al; Diabetic Retinopathy Clinical Research Network. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N Engl J Med*. 2015;372(13):1193-1203. doi:10.1056/NEJMoa1414264
21. Gonzalez VH, Wang PW, Ruiz CQ. Panretinal Photocoagulation for Diabetic Retinopathy in the RIDE and RISE Trials: Not "1 and Done". *Ophthalmology*. 2021;128(10):1448-1457. doi:10.1016/j.ophtha.2019.08.010
22. Bressler NM, Beaulieu WT, Glassman AR, et al; Diabetic Retinopathy Clinical Research Network. Persistent Macular Thickening Following Intravitreous Aflibercept, Bevacizumab, or Ranibizumab for Central-Involved Diabetic Macular Edema With Vision Impairment: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Ophthalmol*. 2018;136(3):257-269. doi:10.1001/jamaophthalmol.2017.6565
23. Kinuthia UM, Wolf A, Langmann T. Microglia and Inflammatory Responses in Diabetic Retinopathy. *Front Immunol*. 2020;11:564077. doi:10.3389/fimmu.2020.564077
24. Rübsam A, Parikh S, Fort PE. Role of Inflammation in Diabetic Retinopathy. *Int J Mol Sci*. 2018;19(4):942. doi:10.3390/ijms19040942