DOI: 10.14744/eer.2023.43153
Eur Eye Res 2023;3(1):1–6

EUROPEAN EYE RESEARCH

ORIGINAL ARTICLE

Efficacy of intravitreal aflibercept monotherapy in treatment naive cases with diabetic macular edema

Sefik Can Ipek, Nilufer Kocak, Mahmut Kaya, Taylan Ozturk, Suleyman Kaynak

Department of Ophthalmology, Dokuz Eylul University Faculty of Medicine, Izmir, Türkiye

Abstract

Purpose: Incidence of diabetes mellitus (DM) increases rapidly in our country as well as around the world, posing a serious threat to public health. Diabetic retinopathy (DR) is the most common microvascular complication in patients with DM since microvascular damage secondary to chronic hyperglycemia starts affecting retina in the early stages of the disease. Our aim is to evaluate the real-life outcomes of intravitreal aflibercept monotherapy in treatment naive cases with diabetic macular edema (DME).

Methods: This study was retrospective case–control study. Medical charts of 75 treatment naive cases with DME were reviewed retrospectively. A total of 127 eyes that received intravitreal aflibercept monotherapy between January 2017 and December 2018 in our Retina Unit were enrolled. Demographics and the results of their initial and all follow-up ophthalmologic examinations as well as the number and frequency of intravitreal shots were noted for each participant. Chi-square, Mann–Whitney U, and Wilcoxon signed-rank tests were used for statistical analysis.

Results: Of the total 75 patients with a mean age of 61.2±10.4 years, 38 (50.7%) were male. Mean follow-up period was 10.2±6.3 months. Mean baseline best-corrected visual acuity and central macular thickness scores were 56.8±19.9 ETDRS letters and 397.8±162.4 µm, whereas they were found as 67.9±16.9 ETDRS letters and 311.0±116.8 µm at the last visit ($p<0.001$ and $p<0.001$, respectively). Aflibercept monotherapy was found to provide better anatomic prognosis in eyes with serous macular detachment ($p<0.001$), and better anatomic as well as functional prognosis in eyes without any concomitant vitreomacular interface disorders ($p=0.037$ and $p=0.042$, respectively).

Conclusion: Intravitreal aflibercept monotherapy proves to be an effective and reliable treatment option in treatment-naive DME cases, even in those with marked optical coherence tomography biomarkers indicating poor outcomes.

Keywords: Aflibercept; central macular thickness; diabetic macular edema; serous macular detachment; visual acuity.

Incidence of diabetes mellitus (DM) increases rapidly in our country as well as around the world, posing a serious threat to public health. Diabetic retinopathy (DR) is the most common microvascular complication in patients with DM since microvascular damage secondary to chronic hyperglycemia starts affecting retina in the early stages of the disease.[1] Vascular endothelial growth factor (VEGF) and other cytokines, which are secreted secondary to capillary ischemia, disrupt extracellular fluid balance, and damage the blood-retina barrier, resulting in diabetic macular

Cite this article as: Ipek SC, Kocak N, Kaya M, Ozturk T, Kaynak S. Efficacy of intravitreal aflibercept monotherapy in treatment naive cases with diabetic macular edema. Eur Eye Res 2023;3(1):1-6.

Correspondence: Sefik Can Ipek, M.D. Department of Ophthalmology, Dokuz Eylul University Faculty of Medicine, Izmir, Türkiye
Phone: +90 232 412 98 98 **E-mail:** sefikcanipek@gmail.com
Submitted Date: 02.12.2022 **Revised Date:** 17.01.2023 **Accepted Date:** 08.02.2023

edema (DME). DME can be seen at any stages of DR, and it is the most common cause of vision loss in diabetics.[2]

Before the new century, laser photocoagulation therapy was used as the standard treatment of DME.[3] As a result of the pursuit of new treatments in response to the increased burden of the disease, agents to block VEGF molecule that plays an important role in the pathophysiology of the disease have been introduced. Various clinical studies have proven their efficacy and reliability over macular edema, so intravitreal anti-VEGF injections have accepted as the standard treatment of DME today.[4] Being the latest approved agent in the treatment of DME, aflibercept is an anti-VEGF agent of fusion protein structure, which has a high affinity against all isoforms of VEGF including placenta-derived growth factor. The VIVID and VISTA studies demonstrated its efficacy and safety in DME treatment, suggesting the superiority of aflibercept monotherapy over laser treatment.[1] According to DR Clinical Research Network (DRCR.net) Protocol T study, aflibercept treatment was found to be as effective as ranibizumab and bevacizumab injections in DME, providing better results especially in patients with low baseline visual acuity in a 1-year follow-up. However, intravitreal injection of aflibercept molecule ensures better visual acuity results when compared to ranibizumab group in the 1st year of follow-up, the superiority observed in aflibercept group was squared in the 2nd year.[5] In this study, we aimed to present our real-life data of aflibercept treatment, which was used as the first choice in treatment-naive DME cases.

Materials and Methods

Medical charts of 127 treatment naive eyes of 75 patients with DME that received intravitreal aflibercept monotherapy between January 2017 and December 2018 in our Retina Unit were reviewed retrospectively. This study followed the ethical principles of the Helsinki Declaration and was approved by the Dokuz Eylül University Institutional Ethics Committee (Approval date and number: 2018/10–14).

Participants underwent detailed ophthalmological examination including best-corrected visual acuity (BCVA) assessment with ETDRS chart, slit-lamp biomicroscopy, intraocular pressure (IOP) measurements using Goldmann applanation tonometer, dilated fundoscopy with a 90D non-contact lens or an indirect binocular ophthalmoscope, and spectral-domain optical coherence tomography (SD-OCT) scans (Spectralis; Heidelberg Engineering) at baseline and all follow-up visits scheduled 4 weeks intervals. Fluorescein angiography (FA) was performed at baseline and all required visits. All study eyes received aflibercept monotherapy according to pro-re-nata (PRN) protocol after three loading doses. It was recommended to administer monthly treatment until BCVA was stabilized or anatomical findings improved on SD-OCT.

Inclusion Criteria

The study group was comprised DME patients with the age of over than 18 years who received intravitreal aflibercept monotherapy. Cases with other ophthalmic disorders except for refractive errors, and those had the history of laser photocoagulation or any intraocular surgeries excluding phacoemulsification, as well as patients who previously received intravitreal and/or subtenon steroids injections were excluded from the study. Written informed consent was obtained from all participants for study participation.

Intravitreal Injection Technique

Intravitreal injections were applied in the operating theater. After applying proparacaine hydrochloride (Alcaine®, Alcon, Türkiye) as a topical anesthetic, the eye was covered with a sterile drape after maintaining skin antisepsis with 10% povidone-iodide in sterile conditions. Sterile eye speculum was placed, and 5% povidone-iodine solution was applied onto the cornea and conjunctiva followed by a 5-min waiting time. Aflibercept of 2 mg/0.05 ml was injected into central vitreous with a 30G needle 4mm from the limbus in phakic eyes and 3.5mm from the limbus in pseudophakic eyes. A sterile cotton swab was used to pressurize the injection point while pulling away the needle after injection. The eye was closed after applying 5% povidone-iodine solution. The patients were prescribed with fusidic acid (Fucithalmic®, Abdi Ibrahim, Türkiye) to be used as 2×1 drops for 4 days. In all cases, anterior segment was examined by slit-lamp biomicroscope in the postinjection 1st day. All participants were also reexamined in the 1st week and 1st month of intravitreal shots.

Data Review

Demographic data, DM history, results of detailed ophthalmologic examinations including BCVA, IOP, and central macular thickness (CMT) scores as well as fundoscopic and FA findings were recorded for initial and every control visits. The systemic and ocular side effects related with intravitreal aflibercept injection were also noted from the medical charts of the participants. Subgroup analyses were performed in eyes with serous macular detachment (SMD) as well as those with vitreomacular interface (VMI) disorders.

Statistical Analysis

The statistical analysis was performed with SPSS 22.0 for Windows statistical package program (SPSS Inc., Chicago, IL, USA). The average, minimum, maximum, and SD values were used as descriptive statistics for continuous variables. After performing Shapiro–Wilk test to check data distribution, Wilcoxon signed-ranks test was used to compare the statistical differences in BCVA and CMT scores between the initial and final control visits. The variables between the study subgroups were examined with Mann–Whitney U-test, and comparison results are given in the tables. Chi-square test was performed to make categorical comparisons. A $p<0.05$ was accepted as significant.

Results

Of the total 75 patients with a mean age of 61.2±10.4 years (range, 21–79 years), 37 (49.3%) were female and 38 (50.7%) were male. The mean duration of DM was 13.9±7.4 years (range, 1–40 years) and the mean follow-up period was 10.2±6.3 months (range, 3–24 months). Among our study, population consisted of 127 treatment-naive eyes with the diagnosis of DME, mean BCVA scores were 56.8±19.9 and 67.9±17.0 ETDRS letters in the initial and final examinations, respectively ($p<0.001$). The mean number of intravitreal injections was 4.6±2.4 (range, 3–14). The mean CMT scores were found as 397.8±162.4 μm (range, 194–1227 μm) at baseline, and 311.0±116.8 μm (range, 108–702 μm) in the final visit ($p<0.001$).

Initial SD-OCT scans depicted a SMD in 36 eyes (28.3%). In the subgroup of eyes with SMD, the mean initial BCVA and CMT scores were 48.8±19.7 ETDRS letters and 490.9±171.4 μm (range, 280–888 μm), whereas they were found as 62.9±19.5 ETDRS letters and 345.9±135.3 μm (range, 183–702 μm) at the final visit. Improvements in BCVA and CMT scores in eyes with or without SMD are given in Table 1. Statistical analyses of the changes between initial and final scores revealed better anatomic prognosis in eyes with SMD after intravitreal aflibercept monotherapy ($p<0.001$); however, there was no statistical difference in functional prognosis between two subgroups ($p=0.152$).

Initial SD-OCT scans were also evaluated for concomitant VMI disorders including epiretinal membrane, vitreomacular adhesion, or traction. In the subgroup of eyes with VMI, an epiretinal membrane was detected in 16 eyes (12.6%), a vitreomacular adhesion was detected in 11 eyes (8.7%), and a vitreomacular traction was detected in three eyes (2.4%). A VMI disorder was detected in 30 eyes (23.6%), in which the mean baseline BCVA and CMT scores were found to be 47.0±26.0 ETDRS letters and 469.6±195.9 μm (range, 237–1227 μm); whereas they were 53.8±22.6 ETDRS letters and 396.9±153.0 μm (range, 186–702 μm) at the last follow-up visit. Improvements in BCVA and CMT scores in eyes with or without a VMI disorder are given in Table 2. Furthermore, a subgroup analyses between VMI disorders are given in Table 3. There was no statistical difference between VMI disorders subgroups. Statistical analyses of the changes between initial and final scores revealed better

Table 1. The BCVA and CMT changes in study eyes with or without SMD

	Eyes with SMD (n=36)	Eyes without SMD (n=91)	p-value
Initial BCVA score (ETDRS letters)	48.8±19.7	56.8±19.9	0.002
Final BCVA score (ETDRS letters)	62.9±19.5	67.9±16.9	0.050
Delta BCVA score (ETDRS letters)	14.3±12.0	9.9±13.7	0.152
Initial CMT score (μm)	490.9±171.4	361.0±143.8	<0.001
Final CMT score (μm)	345.9±135.3	297.2±106.3	0.067
Delta CMT score (μm)	−145.0±170.6	−63.8±114.9	<0.001

BCVA: Best-corrected visual acuity; CMT: Central macular thickness; SMD: Serous macular detachment; Delta: Change between the initial and final scores.

Table 2. The BCVA and CMT changes in eyes with or without any concomitant VMI disorders

	Eyes with any VMI disorders (n=30)	Eyes without any VMI disorders (n=97)	p-value
Initial BCVA score (ETDRS letters)	47.0±26.0	58.7±18.1	0.141
Final BCVA score (ETDRS letters)	53.8±22.6	69.8±15.0	0.027
Delta BCVA score (ETDRS letters)	6.2±16.2	11.3±13.5	0.042
Initial CMT score (μm)	469.6±195.9	375.6±144.6	0.003
Final CMT score (μm)	396.9±153.0	284.4±88.4	<0.001
Delta CMT score (μm)	−65.7±178.5	−95.2±122.7	0.037

BCVA: Best-corrected visual acuity; CMT: Central macular thickness; VMI: Vitreomacular interface; Delta: Change between the initial and final scores.

Table 3. The BCVA and CMT changes in eyes with a VMI disorders

	Group 1 Eyes with ERM (n=16)	Group 2 Eyes with VMA (n=11)	Group 3 Eyes with VMT (n=3)	p-value (1 vs 3)	p-value (1 vs 2)	p-value (2 vs 3)
Initial BCVA score (ETDRS letters)	46.9 ± 26.0	52.8 ± 22.8	61.70 ± 23.6	.377	.554	.564
Final BCVA score (ETDRS letters)	53.8 ± 22.6	69.6 ± 17.8	73.06 ± 7.5	.172	.065	.757
Delta BCVA score (ETDRS letters)	+ 6.8 ± 25.7	+ 16.8± 23.9	11.3 ± 18.2	.778	.319	.723
Initial CMT score (μm)	513.8 ± 237.3	435.8 ± 127.6	358.0 ± 109.2	.288	.330	.357
Final CMT score (μm)	433.9 ± 151.5	338.1 ± 121.2	415.0 ± 251.3	.859	.093	.450
Delta CMT score (μm)	- 79.9 ± 216.6	- 97.6 ± 109.0	+57.0±145,76	.314	.805	.063

BCVA: Best-corrected visual acuity; CMT: Central macular thickness; VMI: Vitreomacular interface; Delta: Change between the initial and final scores; ERM: Epiretinal membrane; VMA: Vitreomacular adhesion; VMT: Vitreomacular traction.

anatomic and functional prognosis in eyes without any VMI disorders after intravitreal aflibercept monotherapy (p=0.037 and p=0.042, respectively). The existence of SMD was detected in 11 eyes (36.7%) in cases with VMI disorders. Initial findings and treatment responses are similar between SMD subgroups in cases with VMI disorders.

Discussion

Macular focal and grid laser application was considered the gold standard treatment in DME management before the widespread usage of anti-VEGF agents.[6] As the effects of inflammatory cytokines and especially VEGF in DME pathogenesis were proven, intravitreal injectable forms of anti-VEGF drugs have been developed for treatment purposes. According to the encouraging results of many studies, intravitreal anti-VEGF injections have become the standard DME treatment today. Comparing to laser treatment, their superior efficacy over anatomic and functional prognosis in eyes with the diagnosis of DME has been reported.[4–8] Today, ranibizumab and aflibercept are the licensed anti-VEGF agents for DME treatment, while bevacizumab can also be used as an off-label drug.

VIVID and VISTA studies have proven that intravitreal aflibercept injection has been more effective in anatomic and functional prognosis of eyes with DME compared to macular laser therapy. Extension studies determined that this effect also continued in the long-term.[1] In these studies, an average of 9–12 injections were applied annually. However, recent real-life data apart from randomized clinical trials have shown fewer annual numbers for intravitreal shots.[7–10] In their 1-year real-life study, Kaiho et al.[8] reported the average number of intravitreal aflibercept injections in their study eyes with DME as being 3.8±2.4 annually. Despite the lower injection frequency, the authors reported successful anatomical and functional results in their cohort. In our study, we followed up treatment-naive DME patients for a mean of 10.2 months, and they received 4.6 intravitreal aflibercept injections on average. In spite of our relatively fewer number of intravitreal aflibercept shots, statistically significant visual gain as well as CMT reduce were acquired. Our results have also supported that aflibercept monotherapy could ensure anatomic and functional response in treatment-naive eyes with the diagnosis of DME within the short-term. Randomized clinical trials have revealed that DME cases require numerous intravitreal injections especially within the 1st year of their treatment. Nevertheless, increased number of intravitreal shots carries the need of more frequent control visits composing extra medical costs, and all of which deteriorate patient comfort. Furthermore, the risk of post-injection endophthalmitis rises cumulatively with the increased number of intravitreal shots.[11,12]

Some studies have reported that SMD and subretinal fluid indicates increased inflammatory burden in DME.[12–14] Recent studies have also defined such OCT findings as a biomarker that may be related with poor visual prognosis.[15,16] Ozdemir et al.[17] reported the frequency of SMD as 31% in their study population with DME. Aggarwal et al.[18] published the relation of SMD evidence on OCT with cystoid type edema and higher CMT scores. No statistical difference was found in anatomic and functional outcomes between the eyes with or without SMD in a previous study evaluating the efficacy of ranibizumab injections at the end of the 1st year of treatment. The authors attributed better visual outcome that was achieved among diabetic eyes with SMD to lower initial BCVA scores. In our study, 28.6% of the studied eyes had SMD on their initial SD-OCT scans. However, baseline BCVA of those eyes was found to be lower than the remaining group and they had gained approximately a mean of 4.5 ETDRS letters more than the eyes without SMD, this did not reach a statistical difference. On the other hand, CMT of eyes with SMD was found to

be higher than the remaining group at the initial as well as final visits; and statistically significantly higher CMT reduce between the first and last control visits was found in eyes with SMD. Better anatomic outcomes achieved with intravitreal aflibercept monotherapy in eyes with SMD may be related with prompt cessation of VEGF effects over a more inflamed retinal tissue.[19–21]

It is very well known that VMI disorders contribute to the success of any anti-VEGF treatments, and literature shows that the anatomic and functional prognosis of such patients is worse. In a study consisted of 105 eyes with DME, Kulikov et al.[22] reported that VMI disorders had reduced anatomical response to anti-VEGF treatment. Based on OCT scans, Battaglia et al.[23] classified the eyes with DME according to possible pathogenesis as vasogenic, non-vasogenic, tractional, and mixed. The authors concluded that eyes with vitreoretinal traction secondary to VMI disorders had the poorest visual acuity scores. In accordance with the literature, we also found lower BCVA as well as thicker CMT scores in eyes with VMI disorders at both baseline and the final visits. Furthermore, eyes with any concomitant VMI disorders had gained approximately a mean of 5.1 ETDRS letters less than the remaining eyes with DME after intravitreal aflibercept regimen. A statistically significantly lower CMT reduce between the first and last control visits was also found in eyes with both DME and VMI disorder.

In our study, the main side effects of intravitreal aflibercept monotherapy seen our study population were subconjunctival hemorrhage and ocular irritation. We did not observe any serious ocular or systemic side effects. The major limitations of the present study are its retrospective design and the lack of a control group. Evaluating a relatively small cohort with treatment-naive cases with DME is the other limitation of this study.

Conclusion

Aflibercept monotherapy provides higher anatomic and functional prognosis in eyes with DME, even in those with marked OCT biomarkers indicating poor outcomes. However, diabetic maculopathy complicated with any VMI disorders is related with the lower anatomic and functional prognosis after anti-VEGF injections, and surgical treatment options ought to be considered in addition to aflibercept monotherapy for such patients.

Ethics Committee Approval: This study was approved by Dokuz Eylul University Non-interventional Clinical Research Ethics Committee (date: 12.04.2018; number: 2018/10-14).

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: S.C.I., N.K., S.K.; Design: S.C.I., N.K., S.K.; Supervision: N.K., M.K., S.K.; Resource: S.C.I.; Materials: S.C.I., M.K., T.O.; Data Collection and/or Processing: S.C.I.; Analysis and/or Interpretation: S.C.I., N.K., M.K., T.O., S.K.; Literature Search: S.C.I.; Writing: S.C.I., T.O.; Critical Reviews: N.K., M.K., T.O., S.K.

Conflict of Interest: None declared.

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

References

1. Heier JS, Korobelnik JF, Brown DM, Schmidt-Erfurth U, Do DV, Midena E, et al. Intravitreal aflibercept for diabetic macular edema: 148-week results from the VISTA and VIVID studies. Ophthalmology 2016;123:2376–85. [CrossRef]
2. Antonetti DA, Klein R, Gardner TW. Diabetic retinopathy. N Engl J Med 2012;366:1227–39. [CrossRef]
3. Photocoagulation for diabetic macular edema. Early treatment diabetic retinopathy study report number 1. Early treatment diabetic retinopathy study research group. Arch Ophthalmol 1985;103:1796–806. [CrossRef]
4. Elman MJ, Qin H, Aiello LP, Beck RW, Bressler NW, Ferris Fl 3rd, et al. Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: Three-year randomized trial results. Ophthalmology 2012;119:2312–8. [CrossRef]
5. Cai S, Bressler NM. Aflibercept, bevacizumab or ranibizumab for diabetic macular oedema: Recent clinically relevant findings from DRCR.net Protocol T. Curr Opin Ophthalmol 2017;28:636–43. [CrossRef]
6. Rodriguez M, Storey P, Do DV. Anti-VEGF therapy for the management of diabetic macular edema. Curr Ophthalmol Rep 2013;1:122–7. [CrossRef]
7. Urbančič M, Klobučar P, Zupan M, Urbančič K, Lavrič A. Anti-VEGF treatment of diabetic macular edema: Two-year visual outcomes in routine clinical practice. J Ophthalmol 2020;2020:6979758. [CrossRef]
8. Kaiho T, Oshitari T, Tatsumi T, Takatsuna Y, Arai M, Shimizu N, et al. Efficacy of one-year treatment with aflibercept for diabetic macular edema with practical protocol. Biomed Res Int 2017;2017:7879691. [CrossRef]
9. Bhandari S, Nguyen V, Fraser-Bell S, Mehta H, Viola F, Baudin F, et al. Ranibizumab or aflibercept for diabetic macular edema: Comparison of 1-year outcomes from the fight retinal blindness! registry. Ophthalmology 2020;127:608–15. [CrossRef]
10. Kiss S, Malangone-Monaco E, Wilson K, Varker H, Stetsovsky D, Smith D, et al. Real-world injection frequency and cost of ranibizumab and aflibercept for the treatment of neovascular age-related macular degeneration and diabetic macular edema. J Manag Care Spec Pharm 2020;26:253–66. [CrossRef]
11. Schwartz SG, Flynn HW JR., Scott IU. Emerging drugs for diabetic macular edema. Expert Opin Emerg Drugs 2014:19:397–405. [CrossRef]
12. Chung YR, Lee SY, Kim YH, Byeon HE, Kim JH, Lee K. Hyper-

reflective foci in diabetic macular edema with serous retinal detachment: Association with dyslipidemia. Acta Diabetol 2020;57:861–6. [CrossRef]
13. Vujosevic S, Toma C, Villani E, Muraca A, Torti E, Florimbi G, et al. Diabetic macular edema with neuroretinal detachment: OCT and OCT-angiography biomarkers of treatment response to anti-VEGF and steroids. Acta Diabetol 2020;57:287–96.
14. Yaya O, Taş İ, Ayrancıoğlu BN, Önder F. The frequency of serous macular detachment in diabetic macular edema. Turk J Ophthalmol 2015;45:92–6. [CrossRef]
15. Ercalik NY, Imamoglu S, Kumral ET, Yenerel NM, Bardak H, Bardak Y. Influence of serous retinal detachment on the outcome of ranibizumab treatment in diabetic macular oedema. Cutan Ocul Toxicol 2018;37:324–7. [CrossRef]
16. Yenihayat F, Özkan B, Kasap M, Karabaş VL, Güzel N, Akpınar G, et al. Vitreous IL-8 and VEGF levels in diabetic macular edema with or without subretinal fluid. Int Ophthalmol 2018;39:821–8. [CrossRef]
17. Ozdemir H, Karacorlu M, Karacorlu S. Serous macular detachment in diabetic cystoid macular oedema. Acta Ophthalmol Scand 2005;83:63–6. [CrossRef]
18. Aggarwal K, Dogra MR, Sanghi G, Gupta V, Singh R, Gupta A. Correlation of ocular and systemic factors with the presence of serous retinal detachment in diabetic macular edema. Adv Ophthalmol Vis Syst 2017;7:00242. [CrossRef]
19. Ozkaya A, Demir G, Kirmaci A. Comparison of aflibercept and ranibizumab in diabetic macular edema associated with subretinal detachment. Eur J Ophthalmol 2020;30:363–9. [CrossRef]
20. Korobelnik JF, Lu C, Katz TA, Dhoot DS, Loewenstein A, Arnold J, et al. Effect of baseline subretinal fluid on treatment outcomes in VIVID-DME and VISTA-DME studies. Ophthalmol Retina 2019;3:663–9. [CrossRef]
21. Kaldırım H, Yazgan S, Kirgiz A, Atalay K, Savur F. A comparison study of ranibizumab and aflibercept in patients with naive diabetic macular edema in presence of serous retinal detachment. Curr Eye Res 2019;44:987–93. [CrossRef]
22. Kulikov AN, Sosnovskii SV, Berezin RD, Maltsev DS, Oskanov DH, 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. [CrossRef]
23. Battaglia MP, Iacono P, Cascavilla M, Zucchiatti I, Bandello F. A pathogenetic classification of diabetic macular edema. Ophthalmic Res 2018;60:23–8. [CrossRef]