Journal of Clinical & Experimental Ophthalmology

Telbizova-Radovanova et al., J Clin Exp Ophthalmol 2014, 5:5
DOI: 10.4172/2155-9570.1000355

Research Article Open Access

# Optical Coherence Tomography Patterns in Diabetic Macular Edema can Predict the Effectiveness of Intravitreal Bevacizumab Combined with Macular Photocoagulation

Karolina Telbizova-Radovanova*, Evdokia Ilieva **and** Iva Petkova

***University Eye Hospital Zora, Sofia, Bulgaria***

***Corresponding author:** Karolina Telbizova-Radovanova, Eye Hospital ZORA, Bul. Maria Luiza 191, DKC № 7, Sofia 1233, Bulgaria, Tel: +359 888982257; E-mail: karolina1973@hotmail.com

**Received date:** May 25, 2014, **Accepted date:** Sep 15, 2014, **Published date:** Sep 18, 2014



## Abstract

**Purpose:** To compare the effectiveness of intravitreal bevacizumab (IVB) combined with macular photocoagulation (MPC) for the treatment of patients with different optical coherence tomography (OCT) patterns of diabetic macular edema.

**Methods:** In this prospective study were included 72 eyes of 58 patients with nonproliferative diabetic retinopathy (NPDR) and nontractional DME with central macular thickness (CMT) over 300 μm. The eyes were categorized into three groups according to OCT features: 22 eyes with diffuse retinal thickening (DRT), 30 eyes with cystoid macular edema (CME), 20 eyes with serous retinal detachment (SRD). All patients received a single dose (1.25mg/0.05ml) of IVB. MPC was applied one month later (25-30 days). Early Treatment Diabetic Retinopahty Study ( ETDRS) best corrected visual acuity (BCVA) and CMT were assessed before and after the treatment (in the 1st, 3rd and 6th month).

**Results:** At month 6, mean BCVA changed with +8.27 ± 10.7 ETDRS letters (P=0.074), -0.97 ± 8.2 ETDRS letters (P=0.351) and +1.8 ± 10.1 ETDRS letters (P=0.925), respectively, for DRT, CME and SRD groups. Mean CMT decreased by 80.7 ± 65.7 μm (P=0.003) in DRT group, by 24.5 ± 104.6 μm (P=0.909) in CME group and by 51.7 ± 124.3 μm (P=0.580) in SRD group. The DRT group was associated with superior BCVA improvement and greater reduction in CMT as compared with the CME and SRD groups.

**Conclusions:** Intravitreal injection of bevacizumab combined with MPC is more effective in the DRT pattern than in the CME or SRD patterns of DME. The pattern of DME shown by OCT may predict the effectiveness of combination treatment.

**Keywords:** Diabetic macular edema; Optical coherence tomography; Anti-VEGF; Intravitreal bevacizumab; Macular photocoagulation.

## Introduction

Diabetic macular edema (DME) is the leading cause of vision impairment in the diabetic population which leads to visual disability when therapy is delayed or applied improperly. Fifteen years ago, there were only three methods to reduce the risk of DME-induced vision loss: laser photocoagulation (LPC) [1], intensive glycemic control [2] and blood pressure control [3]. As a large portion of patients with DME treated with LPC did not show improvement of visual acuity [1,4,5], other methods of treatment began to be applied, including pharmacological agents , surgery, combined therapy, genetic therapy.

Intravitreal corticosteroid application was among the first effective pharmacological methods for the treatment of DME. Many authors [6-10] found that intravitreal injection of triamcinolone has a short-term positive effect on diffuse and persisting DME after laser therapy, but its application leads to local complications like raised intraocular pressure and development of cataract [6,10].

The application of VEGF inhibitors is a relatively new therapy with proven effect which is widely used because it is tolerated well and because of its low risk of systemic and eye complications [11-17].

It is known that VEGF is a key factor in DME pathogenesis, but it is not the only one and its inhibition alone is not sufficient for its effective treatment. Additional studies are necessary to resolve some important matters such as optimum dosage, duration of treatment, safety of years of application, combination with other treatment and dependence on OCT patterns of edema.

The combination of MPC with intavitreal drugs, such as anti-VEGFs or corticosteroids, is one of the alternatives for nontractional DME treatment. Theoretically, this treatment should be more effective than either MPC or intravitreal drugs alone. It is known that intravitreal application of anti-VEGF leads to quick but short-term reduction of DME, while the effect of MPC comes later and lasts longer. Combining these, i.e. the application of MPC in the 4th week after the intravitreal anti-VEGF, when the edema has been reduced to a maximum [14,17], should extend the effect of the treatment and prevent subsequent intravitreal injections.

The purpose of the present study is to compare the effectiveness of IVB combined with MPC for the treatment of patients with different OCT patterns of diabetic macular edema.

## Material and Methods

The present study included 72 eyes of 58 patients with nonproliferative diabetic retinopathy and nontractional DME with central macular thickness (CMT) over 300 μm. The eyes were categorized into three groups according to OCT classification of Otani et associates [18]: group I-22 eyes (21 patients) with diffuse retinal thickening (DRT), group II-30 eyes (23 patients) with cystoid macular edema (CME), group III-20 eyes (14 patients) with serous retinal detachment (SRD).

The study protocol and its probable safety and efficacy of the interventions were explained to all participants before enrollment. The study was approved by the Ethics Committee of our hospital, and informed consent was obtained from all patients.

Exclusion criteria included diabetes mellitus type 1, previous intraocular surgical intervention or intravitreal injection, previous laser photocoagulation within 6 months, macular edema with a different etiology, other diseases of the retina, glaucoma, inflammatory diseases, and significant media opacities.

All patients received a single dose (1.25 mg/0.05 ml) of intravitreal Bevacizumab (Avastin; Genentech Inc., San Francisco, CA, USA). MPC was applied one month later (25-30 days).

Complete ophthalmological examination was conducted before treatment, at month 1, 3 and 6. Examination included BCVA testing using ETDRS charts (in letters and logarithm of minimum angle of resolution (logMAR)), tonometry, non-contact slit-lamp fundus biomicroscopy (+78D lens) and OCT (Stratus,Carl Zeiss Meditec) with measerment the foveal thickness in the central 500 μm diameter area, or the so-called CMT. Fluorescein angiography (FA) was performed at baseline and at month 6.

Statistical analysis was performed with SPSS software package, version 16.0, (Professional Statistics Release, SPSS Inc.). The t-test was used for statistical analysis of changes in BCVA and CMT. A *P*-value of less than 0.05 was considered to be statistically significant.

## Results

In this trial, 72 eyes of 58 patients were enrolled. The general characteristics of each treatment group are summarized in Table 1.

| | DRT | CME | SRD | P among groups |
|---|---|---|---|---|
| Mean age (yrs) ± SD | 61.82±7.15 | 62.9±11.92 | 61.55±9.2 | 0.875 |
| Female/male (No. of eyes) | 8/14 | 12/18 | 5/15 | 0.541 |
| Mean diabetes duration (yrs) ± SD | 9.95 ± 5.8 | 11.73 ± 7.9 | 10.8 ± 7.2 | 0.674 |
| Hypertension (No. of eyes) (%) | 18 (81.8%) | 28 (93.3%) | 18 (90%) | 0.419 |
| HbA1C (%) | 7.24 ± 0.64 | 7.56 ± 0.89 | 7.49 ± 0.74 | 0.333 |
| Insulin dependence (No. of eyes) (%) | 7 (31.8%) | 13 (43.3%) | 11 (55%) | 0.317 |
| SD: Standart Deviation; HbA1C: Glycosylated Hemoglobin; DRT: Diffuse Retinal Thickening; CME: Cystoid Macular Edema; SRD: Serous Retinal Detachment | | | | |

**Table 1:** Distribution of baseline characteristics in each treatment group.

There was no statistically significant difference between the three groups in terms of sex, age, mean diabetes duration, number of eyes with hypertension, HbA1C value and number of eyes with insulin dependence.

The mean BCVA and CMT in each group at every visit and the mean changes in BCVA and CMT from baseline to month 6 are presented in Table 2.

| | DRT | CME | SRD | P among groups |
|---|---|---|---|---|
| Before treatment<br>BCVA (letters ± SD)<br>BCVA (logMAR ± SD)<br>CMT(μm ± SD) | 31.5 ± 12.06<br>0.47 ± 0.24<br>397.82 ± 52.19 | 28.37 ± 12.74<br>0.53 ± 0.25<br>440.3 ± 104.8 | 17.6 ± 11.87<br>0.74 ± 0.23<br>527.85 ± 79.07 | 0.001<br><0.0001 |
| 1st month<br>BCVA (letters ± SD)<br>BCVA (logMAR ± SD)<br>CMT(μm ± SD) | 38.5 ± 12.35<br>0.33 ± 0.24<br>318.0 ± 51.46 | 32.83 ± 13.5<br>0.44 ± 0.27<br>379.1 ± 85.1 | 24.4 ± 17.53<br>0.61 ± 0.35<br>430.25 ± 134.5 | 0.009<br>0.001 |
| 3rd month | 39.6 ± 12.65 | 29.17 ± 11.61 | 22.35 ± 17.94 | 0.001 |

| | | | | |
|---|---|---|---|---|
| BCVA (letters ± SD)<br>BCVA (logMAR ± SD)<br>CMT(μm ± SD) | 0.30 ± 0.25<br>319.59 ± 66.51 | 0.51 ± 0.23<br>410.3 ± 82.9 | 0.65 ± 0.35<br>454.0 ± 140.3 | <0.0001 |
| 6th month<br>BCVA (letters ± SD)<br>BCVA (logMAR ± SD)<br>CMT(μm ± SD) | 39.7 ± 13.35<br>0.30 ± 0.26<br>317.05 ± 77.98 | 27.4 ± 11.41<br>0.55 ± 0.22<br>415.8 ± 95.6 | 19.4 ± 15.11<br>0.71 ± 0.30<br>476.15 ± 124.7 | <0.0001<br><0.0001 |
| BCVA change<br>(0-6 month)<br>(letters ± SD)<br>(logMAR ± SD)<br>P within group<br>CMT change<br>(0-6 month)<br>(μm±SD)<br>P within group | +8.27 ± 10.7<br>-0.16 ± 0.21<br>0.074<br>-80.7 ± 65.7<br>0.003 | -0.97 ± 8.2<br>+0.02 ± 0.16<br>0.351<br>-24.5 ± 104.6<br>0.909 | +1.8 ± 10.1<br>-0.03 ± 0.20<br>0.925<br>-51.7 ± 124.3<br>0.580 | 0.004<br>0.146 |
| BCVA: Best Corrected Visual Acuity; logMAR: Logarithm of Minimum Angle of Resolution; CMT: Central Macular Thickness; SD: Standart Deviation; DRT: Diffuse Retinal Thickening; CME: Cystoid Macular Edema; SRD: Serous Retinal Detachment. | | | | |

**Table 2:** Mean BCVA and CMT of each group before treatment, month 1,3 and 6, and mean change of BCVA and CMT for each group up to month 6.

BCVA improved 1 month after treatment in all three groups. In the DRT group VA improved slightly to month 6. In the CME and SRD groups VA did not change significantly. Mean CMT decreased in all groups, however, the reduction was significantly greater in the DRT group than in the other groups at month 6.

After 6 month of follow-up, 50%, 10% and 10% of eyes, respectively, in DRT, CME and SRD groups, experienced visual improvement of ≥ 10 ETDRS letters, 45.4%, 73.3% and 85% remained stable, and 4.6%, 16.7% and 5% experienced visual worsening of ≥ 10 ETDRS letters (Figure 1).

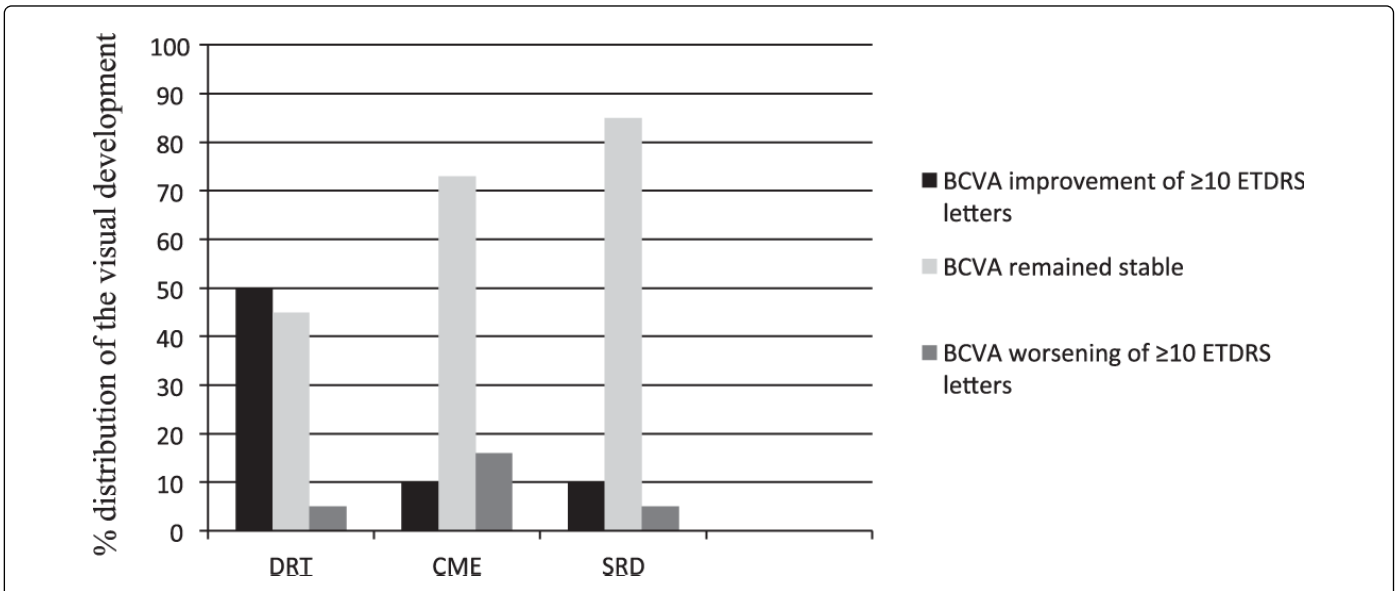


**Figure 1:** The % distribution of the visual development following combination treatment in DRT, CME and SRD groups. DRT: Diffuse Retinal Thickening; CME: Cystoid Macular Edema; SRD: Serous Retinal Detachment.

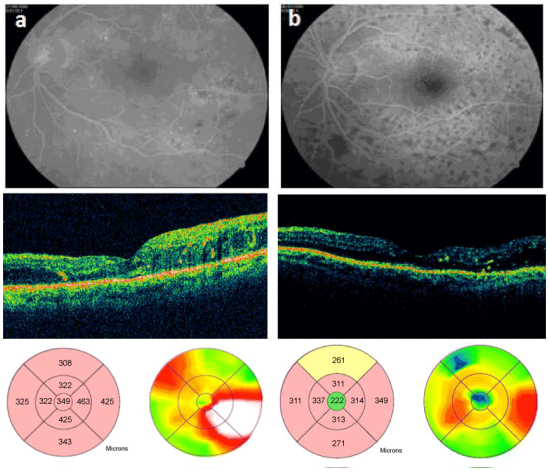


**Figure 2:** Late-phase FA and OCT evaluation at baseline and at final follow-up visit ( month 6) of left eye of 61 year old man with a twelve year history of diabetes and DRT treated with IVB and MPC. a At baseline BCVA was 46 ETDRS letters, CMT was 349 µm . b At month 6 BCVA improved to 52 ETDRS letters, CMT decreased to 222 µm.

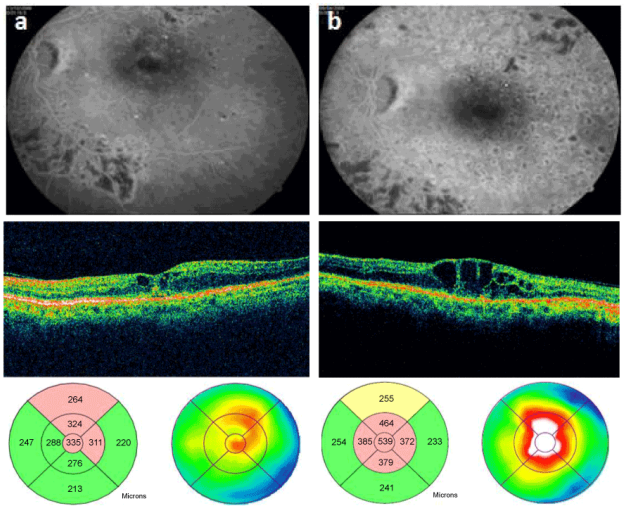


**Figure 3:** Late-phase FA and OCT evaluation at baseline and at final follow-up visit (month 6) of left eye of 68 year old female with a fifteen year history of diabetes and CME treated with IVB and MPC. a At baseline BCVA was 40 ETDRS letters, CMT was 335 µm. b At month 6 BCVA decreased to 30 ETDRS letters, CMT increased to 539 µm.

Figures 2, 3 and 4 show examples of eyes with DRT (Figure 2), CME (Figure 3) and SRD (Figure 4) treated with IVB and MPC.

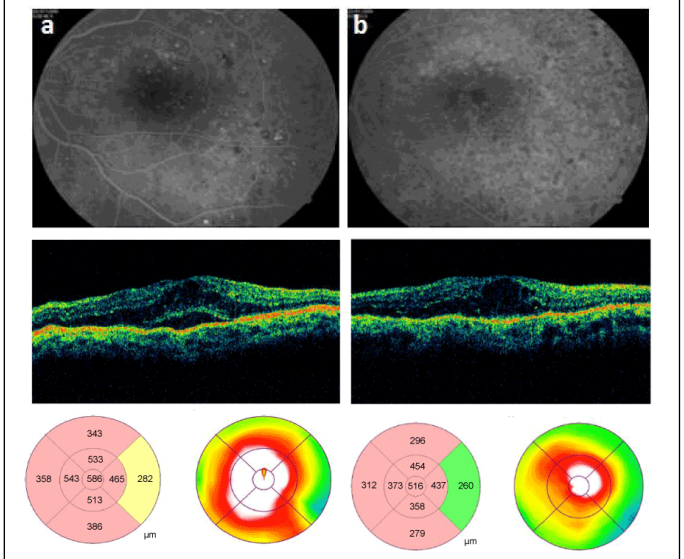


**Figure 4:** Late-phase FA and OCT evaluation at baseline and at final follow-up visit (month 6) of left eye of 52 year old man with diabetes diagnosed three years previously and SRD treated with IVB and MPC. a At baseline BCVA was 36 ETDRS letters, CMT was 586 µm . b At month 6 BCVA after improving returned to the initial level (36 ETDRS letters), CMT decreased to 516 µm.

Mean BCVA in the DRT group increased by 8.27 ± 10.7 ETDRS letters (-0.16 ± 0.21 logMAR), but the change was not statistically significant (P=0.074). In CME group mean BCVA decreased by 0.97 ± 8.2 ETDRS letters (+0.02 ± 0.16 logMAR) (P=0.351). In SRD group mean BCVA increased by 1.8 ± 10.1 ETDRS letters (-0.03 ± 0.20 logMAR) (P=0.925). Mean CMT decreased in all groups, by 80.7 ± 65.7 µm (P=0.003) in DRT group, by 24.5 ± 104.6 µm (P=0.909) in CME group and by 51.7 ± 124.3 µm (P=0.580) in SRD group. Only in DRT group the change was statistically significant (P=0.003).

Comparison of mean BCVA change showed significant difference between the DRT and CME groups (P=0.001), as well as between the DRT and SRD groups (P=0.032). There was no significant difference between the CME and SRD groups (P=0.319).

After 6 months of follow-up, no severe ocular (endophthalmitis, retinal detachment, traumatic cataract) or systemic (thromboembolic events, systemic hypertension) adverse events were reported. Only transitory conjunctival hyperaemia and subconjunctival hemorrhage after the intravitreal application of bevacizumab were observed.

## Discussion

In recent years optical coherent tomography has become the most used diagnostic tool for DME. Today there are several classifications of DME according to the OCT criteria [18-20]. This particular study uses the classification of Otani, according to which nontractional DME is three types: DRT, CME and SRD [18].

In our study we find a correlation between mean BCVA, mean CMT and OCT patterns of DME. The DRT type has better BCVA and lower CMT than other types of DME. The explanation of this may be the histopathologic research showing that the accumulation of liquid

begins with intracytoplasmic swelling of the Müller cells [21]. Persistent edema is followed by liquefaction necrosis of the Müller cells and the adjacent neurons with formation of cystic areas in the retina [21,22]. In some of the eyes with severe cystoid edema there is a confluence of the cystic areas which leads to retinoschistic appearance of the macula and damaging of photoreceptors. These histopathology findings may presumably explain the observed differences in visual acuity between the three types of nontractional DME.

Previous studies demonstrated the effectiveness of laser, intravitreal corticosteroid or anti-VEGF treatment alone of the various OCT types of DME. Kim et al. [23] found that focal laser photocoagulation is the best treatment for DRT. Shimura et al. [24] showed that CME responds best to the treatment with intravitreal triamcinolone acetonide. In respect to monotherapy with IVB, some authors [25,26] concluded that visual acuity outcomes are better in DRT than in CME and SRD. Others [27,28] found that IVB gives the best results in CME.

The beneficial effect of combination treatment with anti-VEGF medication and MPC on patients with DME has been demonstrated in recent published studies without focusing on different initial features of DME [29-32].

There is still not sufficient data about the effect on visual acuity outcomes of the combination treatment with anti-VEGF/MPC depending on OCT patterns of the edema. Lee et al. [33] concluded that the combination treatment with IVB and MPC reduces central macular thickness in all three morphological patterns of edema, but they do not state whether there was a different change of visual acuity in the three groups.

The present study finds that the combination treatment improves BCVA in DRT group, but in CME and SRD, BCVA did not change after 6 months of follow-up. The improvement of BCVA in DRT group was not statistically significant (P= 0.074). The mean CMT after combination treatment decreased in all groups. However, this was statistically significant only in the DRT group (P=0.003). Furthermore the results in DRT group showed a higher number of subjects (50%) achieving visual improvement ≥ 10 ETDRS letters following combination treatment as compared to other groups (10% in CME group and 10% in SRD group).

The present study has several limitations. The follow-up period was relatively short to prove the above conclusions. The small number of patients could be another limitation.

In conclusion, the intravitreal injection of bevacizumab combined with MPC is more effective in the DRT pattern than in the CME or SRD patterns of DME. In DRT type, combination treatment leads to the improvement of BCVA. In CME and SRD types BCVA remains at the initial level until the sixth month following treatment. Therefore, the patterns of DME shown by OCT may predict the effectiveness of combination treatment.

However, a study with a longer follow-up period and larger number of patients should confirm the results of the present study.

## Acknowledgement

This research was supported by University Eye Hospital Zora, Sofia, Bulagaria. No potential conflict of interest relevant to this article was reported.

## References

1. Early Treatment Diabetic Retinopathy Study Research Group (1985) Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. Arch Ophthalmol 103: 1796-1806.
2. Diabetes Control and Complications Trial Research Group (1993) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med 329: 977-986.
3. UK Prospective Diabetes Study Group (1998) Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 317: 703-713.
4. Diabetic Retinopathy Clinical Research Network (2008) A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema. Ophthalmology 115: 1447-1449, 1449.
5. Lee CM, Olk RJ (1991) Modified grid laser photocoagulation for diffuse diabetic macular edema. Long-term visual results. Ophthalmology 98: 1594-1602.
6. Jonas JB, Kreissig I, Söfker A, Degenring RF (2003) Intravitreal injection of triamcinolone for diffuse diabetic macular edema. Arch Ophthalmol 121: 57-61.
7. BatioÄŸlu F, Ozmert E, Parmak N, Celik S (2007) Two-year results of intravitreal triamcinolone acetonide injection for the treatment of diabetic macular edema. Int Ophthalmol 27: 299-306.
8. Gillies MC, Sutter FK, Simpson JM, Larsson J, Ali H, et al. (2006) Intravitreal triamcinolone for refractory diabetic macular edema. Two-year results of a double-masked, placebo-controlled, randomized clinical trial. Ophthalmology 113: 1533-1538.
9. Hauser D, Bukelman A, Pokroy R, Katz H, Len A, et al. (2008) Intravitreal triamcinolone for diabetic macular edema: comparison of 1, 2, and 4 mg. Retina 28: 825-830.
10. Cunningham MA, Edelman JL, Kaushal S (2008) Intravitreal steroids for macular edema: the past, the present, and the future. Surv Ophthalmol 53: 139-149.
11. Nguyen QD, Brown DM, Marcus DM, Boyer DS, Patel S, et al. (2012) Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology 119: 789-801.
12. Soheilian M, Ramezani A, Obudi A, Bijanzadeh B, Salehipour M, et al. (2009) Randomized trial of intravitreal bevacizumab alone or combined with triamcinolone versus macular photocoagulation in diabetic macular edema. Ophthalmology 116: 1142-1150.
13. Shoeibi N, Ahmadieh H, Entezari M, Yaseri M (2013) Intravitreal Bevacizumab with or without Triamcinolone for Refractory Diabetic Macular Edema: Long-term Results of a Clinical Trial. J Ophthalmic Vis Res 8: 99-106.
14. Arevalo JF, Sanchez JG, Lihteh Wu, Maia M, Alezzandrini AA, et al. (2009) Primary intravitreal Bevacizumab (Avastin) for diffuse diabetic macular edema: results from the Pan-American Collaborative Retina Study Group at 24-months follow-up. Ophthalmology 116:1488-1497.
15. Michaelides M, Kaines A, Hamilton RD, Fraser-Bell S, Rajendram R, et al. (2010) A prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT study) 12-month data: report 2. Ophthalmology 117: 1078-1086.
16. OzkiriÅŸ A (2009) Intravitreal bevacizumab (Avastin) for primary treatment of diabetic macular oedema. Eye (Lond) 23: 616-620.
17. Paccola L, Costa RA, Folgosa MS, Barbosa JC, Scott IU, et al. (2008) Intravitreal triamcinolone versus bevacizumab for treatment of refractory diabetic macular oedema (IBEME study). Br J Ophthalmol 92: 76-80.
18. Otani T, Kishi S, Maruyama Y (1999) Patterns of diabetic macular edema with optical coherence tomography. Am J Ophthalmol 127: 688-693.
19. Panozzo G, Parolini B, Gusson E, Mercanti A, Pinackatt S, et al. (2004) Diabetic macular edema: an OCT-based classification. Semin Ophthalmol 19: 13-20.

20. Kim BY, Smith SD, Kaiser PK (2006) Optical coherence tomographic patterns of diabetic macular edema. Am J Ophthalmol 142: 405-412.
21. Yanoff M, Fine BS, Brucker AJ, Eagle RC Jr (1984) Pathology of human cystoid macular edema. Surv Ophthalmol 28 Suppl: 505-511.
22. Fine BS, Brucker AJ (1981) Macular edema and cystoid macular edema. Am J Ophthalmol 92: 466-481.
23. Kim NR, Kim YJ, Chin HS, Moon YS (2009) Optical coherence tomographic patterns in diabetic macular oedema: prediction of visual outcome after focal laser photocoagulation. Br J Ophthalmol 93: 901-905.
24. Shimura M, Yasuda K, Nakazawa T, Hirano Y, Sakamoto T, et al. (2011) Visual outcome after intravitreal triamcinolone acetonide depends on optical coherence tomographic patterns in patients with diffuse diabetic macular edema. Retina 31: 748-754.
25. Shimura M, Yasuda K, Yasuda M, Nakazawa T (2013) Visual outcome after intravitreal bevacizumab depends on the optical coherence tomographic patterns of patients with diffuse diabetic macular edema. Retina 33: 740-747.
26. Kim M, Lee P, Kim Y, Yu SY, Kwak HW (2011) Effect of intravitreal bevacizumab based on optical coherence tomography patterns of diabetic macular edema. Ophthalmologica 226: 138-144.
27. Wu PC, Lai CH, Chen CL, Kuo CN (2012) Optical coherence tomographic patterns in diabetic macula edema can predict the effects of intravitreal bevacizumab injection as primary treatment. J Ocul Pharmacol Ther 28: 59-64.
28. Roh MI, Kim JH, Kwon OW (2010) Features of optical coherence tomography are predictive of visual outcomes after intravitreal bevacizumab injection for diabetic macular edema. Ophthalmologica 224: 374-380.
29. Diabetic Retinopathy Clinical Research Network1, Scott IU, Edwards AR, Beck RW, Bressler NM, et al. (2007) A phase II randomized clinical trial of intravitreal bevacizumab for diabetic macular edema. Ophthalmology 114: 1860-1867.
30. Mitchell P, Bandello F, Schmidt-Erfurth U, Lang GE, Massin P, et al. (2011) The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmology 118: 615-625.
31. Solaiman KA, Diab MM, Abo-Elenin M (2010) Intravitreal bevacizumab and/or macular photocoagulation as a primary treatment for diffuse diabetic macular edema. Retina 30: 1638-1645.
32. Diabetic Retinopathy Clinical Research Network, Elman MJ, Qin H, Aiello LP, Beck RW, et al. (2012) Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: three-year randomized trial results. Ophthalmology 119: 2312-2318.
33. Lee SJ, Kim ET, Moon YS (2011) Intravitreal bevacizumab alone versus combined with macular photocoagulation in diabetic macular edema. Korean J Ophthalmol 25: 299-304.