Effectiveness of Three Loading Dose of Intravitreal Bevacizumab in Central Diabetic Macular Edema

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ABSTRACT

Purpose: To assess efficacy of three loading dose of bevacizumab in central diabetic macular edema.

Materials and Methods: This retrospective study included 30 eyes of 23 patients who were given three loading doses of monthly intravitreal bevacizumab (1.25 mg/mL) for central DDME between February, 2019 and January, 2021. The study included treatment-naive eyes with best-corrected visual acuity (BCVA) ≥ least 5 letters at baseline. In all cases, central macular thickness (CMT) was measured using spectral-domain optical coherence tomography (SD-OCT: Spectralis, Heidelberg Engineering, Heidelberg, Germany). The BCVA was assessed using geometric chart at 4 meters. BCVA, CMT and intraocular pressure measurements as well as biomicroscopy and fundus examination were performed at each control visit. Primary efficacy outcome was visual acuity gain (in letters) and CMT reduction. Data were analyzed using Paired samples t test, ANOVA and Pearson's correlation analysis.

Findings: Mean age was 59.0±8.1 years in the study population. Mean BCVA was 19.6±10.7 letters while mean CMT was 479.0±10.6 µm at baseline. The vision was improved to 22.8±10.1 letters (p=0.007) while mean CMT was decreased t0 453.9±137.9 µm (p=0.163) after first injection (Paired samples t test). The vision was improved to 25.1±9.4 letters (p=0.007) and mean CMT was decreased to 420.8±130.5 µm (p=0.016) after second injection; and 28.6±9.9 letters (p=0.000) and 393±146.0 µm (p=0.002) after third injection. The letter gain was 9 letters. It was found that ≥3 orders improvement was achieved in 9 eyes)30%) whereas 2 orders in 8 eyes (26.7%) and 1 order in 9 eyes (30.0%). There was no response or decreased vision in 4 eyes (13.3%).

Conclusion: Treatment with three loading dose of monthly bevacizumab is an effective first-line treatment ensuring visual and anatomic improvement in DME.

Keywords: Diabetic macular edema, Bevacizumab, Intravitreal injection.

INTRODUCTION

Bevacizumab is a humanized, mouse monoclonal antibody against VEGF-A (93% human, 7% mouse). It leas no immune response in human. It can block all isoforms of vascular endothelial growth factor (VGEF) by its two binding site.[1] It is the first anti-VGEF treatment approved in colorectal cancer by FDA (February, 2004).[2] Since the intraocular administration hasn't been approved, ocular use is off-label. However, it is widely used worldwide due to its efficacy and low cost.[3] In the BOLT study which is the first prospective, randomized clinical trial comparing bevacizumab with traditional laser photocoagulation of macula in the treatment of diabetic macular edema, total of 13 intravitreal bevacizumab (IVB) injections were administered to the patients during 2 years and median visual gain was 9 letters at the end of follow-up period with mean visual improvement of 8,6 letters. In the laser photocoagulation arm, patients underwent 4 laser therapies during 2 years with a mean vision loss was 0.5 letters at the end of follow-up. In the study, IVB was found to be significantly superior to traditional laser photocoagulation. The study was published immediately before approval of ranibizumab in DME (2012).[4]

In this study, it was aimed to investigate efficacy of bevacizumab in DME treatment in treatment-naïve DME patients who received three loading dose of month IVB

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injections as first-line treatment in our clinic by visual and anatomic changes one month after final injection.

MATERIALS AND METHODS

In this retrospective study, we reviewed files of the treatment-naive (no previous anti-VGEF injection or intravitreal dexamethasone implant) patients who diagnosed as diffuse DME involving foveal center by fundus examination and spectral-domain optical coherence tomography (SD-OCT) and received 3 consecutive IVB (1.25 mg/0.05 mL; Avastin /Altuzan 100mg/4ml, Genentech, Roche) injections in the Retina Unit of SBU Bozyaka Teaching and Research Hospital between February, 2019 and January, 2021. The study included 30 eyes of 23 patients with available visual acuity measurements and OCT scans in control visits one month after each injection. All patients included were aged>18 years and had type 1 or type 2 diabetes mellitus. The study was approved by Institutional Ethics Committee (5.5.2021/2021-76). All patients provided Informed Off-Label Treatment Consent. The study was conducted in accordance to tenets of Helsinki Declaration.

The study included patients with baseline visual acuity ≥5 letters who received three loading doses of IVB every 30-45 days. No IVB injection was given to the patients who had history of major cardiovascular or cerebrovascular disease within prior 6 months; intravitreal steroid or focal laser coagulopathy was performed in such patients. In all patients, demographic data, best-corrected visual acuity (BCVA) and central macular thickness (CMT) as measured by SD-OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany) were recorded at baseline. The visual acuity was measured by an independent technician using Eğrilmez charts at 4 meters.[5] In this geometric chart having five letter "E" at each order, visual acuity is rated between 5 and 70 letters (20/200-20/10; decimal: 0.1-2.0); full vision (20/20) corresponds to 55 letters. All patients underwent fundus fluorescein angiography and no IVB loading was performed in eyes with marked foveal avascular zone enlargement and macular ischemia.

In all control visits after each injection, BCVA and CMT values, intraocular pressure as measured by Goldmann applanation tonometry, biomicroscopy and fundus examination as well as local and systemic adverse effects were assessed. Post-treatment data were compared with baseline visual acuity and CMT values to assess efficacy of treatment. Primary efficacy outcome measure was defined as visual acuity gain (in letters) and CMT reduction. The patients with missing injection or data were excluded. Again, patients with vitreomacular traction or epiretinal membrane which may influence on vision on OCT scan, those with previous vitreoretinal surgery or those previously treated for DME were excluded. In addition, patients with media opacity such as cataract or corneal opacity or those with uncontrolled proliferative diabetic retinopathy were also excluded. No IVB injection was administered in patients with visual acuity>35 letters (65 ETDRS letters).

Injection was performed by ophthalmology residences under proparacaine anesthesia in a local operating room with Hepa filter. Using a 5 mL injector, 3 ml bevacizumab was drawn from Altuzan vial (100 mg/4 mL) by an ophthalmology assistant with sterile preparation. The vial was opened by a nurse and disposed after use. Then, the needle was changed and bevacizumab was filled to certain number of insulin injectors (0.3 ml in each). After placing a 30 G needle, doses were adjusted as 0.05 mL (1.25 mg) by removing excess bevacizumab. The patients were transferred to operating room with cap, mask and galosh. The ophthalmologist used cap, mask, sterile gown and gloves. A new set was used for each injection. Ocular region and eyebrows were prepared using povidone iodine and 5% povidone iodine was awaited over conjunctival fornix. Sterile drapes were used. A wire blepharostat was applied as eyebrows being under drape. Then, povidone iodine and local anesthetic was applied to injection site for 10 seconds using a cotton swab. Intravitreal injection was performed via pars plana at a point 4 mm to limbus in phakic eyes and 3.5 mm to limbus in pseudophakic eyes. Silence was maintained during injection procedure. The patient was questioned regarding light perception. After injection, eye was closed using a bandage for 24 hours and levofloxacin eye drop (4x1 for 3-5 days) was prescribed. Injection was postponed in patients with conjunctivitis, blepharitis or high arterial pressure. A control visit on next day was scheduled to assess regarding findings of infection or toxicity.

In the study, primary outcome measure for IVB efficacy was defined as improvement in vision (as letters) on the control visit one month after third injection when compared to baseline. Secondary efficacy outcomes were CMT reduction as measured by OCT, rate of patients with visual gain of 10 letters or 15 letters. Local or systemic adverse effects were also considered. Follow-up visits were scheduled by monthly intervals (±1 week). Vision improvement ≥1 order (5 letters) and CMT reduction was considered as efficacy measure. Unresponsiveness was defined as lack of improvement or 1 order decrease in vision without improvement in OCT findings.

Statistical analysis: Data were analyzed using SPSS version

22.0. Results are presented as mean ± standard deviation. Paired samples t test was used to compare baseline BCVA and CMT values with those obtained at postoperative controls while changes throughout study were assessed using ANOVA test. Pearson's correlation analysis was used to evaluate correlation in subgroups. A $p<0.5$ value was considered as statistically significant.

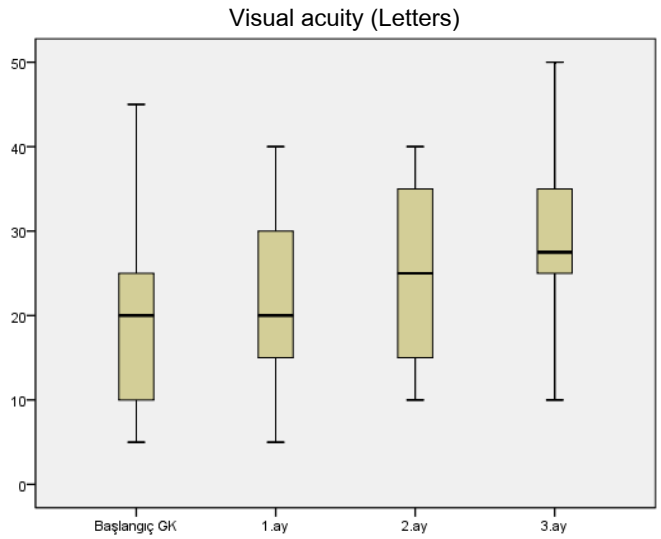
FINDINGS

There were 14 men (60%) and 9 women (40%) in the study; mean age was 59±8 years (47-78 years). Of the eyes included, 17 were left eyes and 13 were right eyes. Mean duration of diabetes mellitus was 12.4±5.5 years. There was hypertension and smoking in one-half of the patients. Throughout study period, focal laser coagulation was performed in 3 eyes (10.0%). Focal laser was performed on week 6 in one eye and on week 8 in two eyes. No adverse effect other than subconjunctival hemorrhage was observed due to injections. No systemic vascular adverse effect was observed. Mean BCVA and CMT was 19.6±10.7 letters (approximately 0.3) and 479.0±10.6 µm at baseline. The BCVA was improved to 22.8±10.1 letters with mean visual gain of 3.2 letters after first injection when compared to baseline (Graphic 1), indicating a significant improvement (p=0.007). The CMT was decreased to 453.9±137.9 µm with mean reduction of 15.1 µm in thickness after first injection but the reduction did not reach statistical significance (p=0.163; Paired samples t test). The BCVA was improved to 25.1±9.4 letters (approximately 0.4) with mean visual gain of 5.5 letters after second injection (p=0.000) while mean CMT was decreased to 420.8±130.5 µm with mean reduction of 58.2 µm in thickness, indicating significant improvement (p=0.016). The BCVA was improved to 28.6±9.9 letters (approximately 0.5) with mean visual gain of 9.0 letters after third injection (p=0.000) while mean CMT was decreased to 393.0±146.0 µm with mean reduction of 86.0 µm in thickness (p=0.020) (Graphic 2). After three bevacizumab injections, visual gain was 9 letters (approximately 2 orders). It was striking that CMT thinning became statistically significant after second injection.

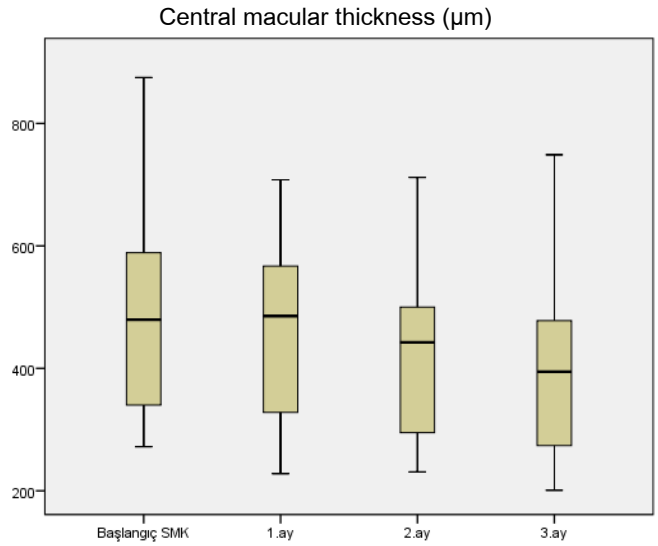
It was found that the visual improvement in consecutive BCVA measurements and CMT reduction were statistically significant ($p<0.001$, for both, ANOVA test). It was found that ≥3 orders improvement was achieved in 9 eyes)30%) whereas 2 orders in 8 eyes (26.7%) and 1 order in 9 eyes (30.0%). There was no change in vision in one eye (3.3%) and decreased vision in 3 eyes (10.0%).

In subgroup analysis (Pearson's correlation analysis), there was no significant correlation between VAs after first injection and second injections (p=0.140) while there was significant correlation between VAs after first and third injection (p=0.000). In addition there was no correlation between CMTs after first and second injections (p=0.057) while there was significant correlation between CMTs after first and third injections. The CMT after third injection was higher in patients with dense macular edema and higher CMT at baseline (p=0.003). No significant correlation was found between CMTs after second and third injections.

No significant correlation was found between baseline BCVA an CMT (p=0.770). However, it was found that baseline BCVA was correlated with BCVAs after first, second and third injections (p=0.007; p=0.000; and p=0.000, respectively). Patients with better baseline



Graphic 1: *Changes in best-corrected visual acuity after first, second and third bevacizumab injections.*



Graphic 2: *Changes in best-corrected visual acuity after first, second and third bevacizumab injections.*

vision maintained their vision during treatment period. It was found that baseline BCVA had no correlation with CMTs after first, second and third injections (p=0.582; p=0.771; and p=0.847, respectively). Again, it was found that baseline CMT had no correlation with BCVAs after first, second and third injections (p=0.220; p=0.263; and p=0.282, respectively). This suggests that visual acuity isn't proportional with macular thickness measured by OCT. It was found that baseline CMT was correlated with CMTs after first, second and third injections (p=0.000; p=0.000; and p=0.001, respectively). Although the patients with dense DME and high CMT values at baseline showed improvement during treatment period, they completed study with relatively higher values.

DISCUSSION

In this retrospective study investigated efficacy of three doses of IVB in DME eyes involving fovea, at least one order improvement was achieved in 86.7% of the cases. A significant reduction was observed in macular edema as demonstrated by OCT (Figure 1). In the study, 46% improvement was achieved in vision together with CMT reduction by 18%. It was observed that there was rapid improvement in vision but anatomic improvement was achieved after second injection. The CMT value of 393 µm at the end of follow-up suggested that edema maintained by 143 µm given the normal CMT is 250 µm. This suggested that maintaining injection might be useful. In fact, annual number of anti-VGEF injections was 10 in average in many studies. In DRCR.net study, 10 IVB injections, 10 intravitreal ranibizumab (IVR) injections and 9 intravitreal aflibercept (IVA) injections were administered in one year.[3] This is mainly due to chronic nature of DME, reduced drug activity within a month and volume of macular fluid. The higher volumes require more injections and time to resolve edema completely. In our study, there was no correlation between baseline visual acuity and CMT. In similar studies, it was shown that CMT isn't a direct measure for visual acuity.[6,7] This is due to there are several factors other than CMT which determine visual acuity such as type of edema, presence of subretinal fluid, bridging bands (Müller cells), disorganization of retinal inner layer (DRIL), macular volume and disruption in ellipsoid zone. Again, it was found that CMT changes after three IVB injections were correlated with baseline CMT but not visual acuity in our study. On contrary, it was found that CMT changes were correlated with baseline visual acuity in DRCRnet study.[3] In a prospective study by Kook et al., at least 3 IVB injections were administered to 48% of 126 eyes which underwent focal laser, panretinal laser, intravitreal triamcinolone or vitrectomy previously.[7] In the eyes with baseline visual acuity of 40.3 letters and CMT of 463 µm, there was 1.6 letters decrease on month 6 while 5.1 letters improvement on month 12. This finding confirmed that IVB has lower efficacy in previously treated eyes. However, CMT was significantly decreased to 374 µm on month 6 and 357 µm on month 12. It was found that IVB is beneficial and does not change diameter of foveal avascular zone in cases without macular ischemia. [7]

Only results after first 3 injections should be considered in order to compare our study with those in the literature. In the DRCR.net study, mean visual gain was 9.7 letters in one

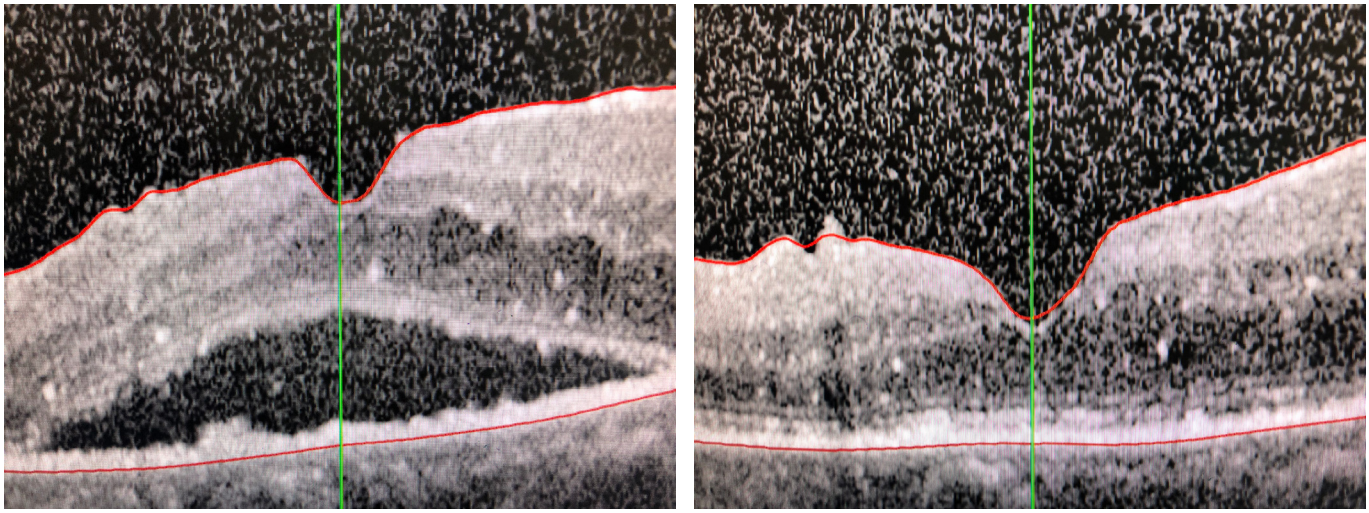


Figure 1: *OCT images of a patient with good response to treeatment.* **A.** Cystic macular edema which is more prominent in outer nuclear layer; hyper-reflective dots; and subretinal fluid (SRF) are seen, **B.** After 3 doses of intravitreal bevacizumab injection, it can be seen that SRF is regressed and foveal margins appeared more markedly. Regular outer limiting membrane and elipsoid zone. It is striking that no improvement in hyper-reflective dots.

year.[3] In our study, the visual gain by 9 letters in 3 months is in agreement with DRCR.net study. Since study population was limited in our study, we did not stratify patients according to baseline visual acuity. However, patients with visual acuity of finger counting were excluded in our study. This is due to fact that measurable vision by letters was primary feature in our study. As known, for patients could not read letters at 4 meters, the chart was placed at 2 meters in order to ensure letter reading in ETDRS study.[4] To compensate distance, 30 letters was added to visual acuity in patients reading letters at 4 meters. When our results were converted to ETDRS, mean baseline visual of 19.6 letters (ETDRS: 49.6) improved to 28.6 letters (ETDRS. 58.6) within 3 months.

In studies conducted before approval of IVR in the treatment of DME (2004-2012), the IVB was shown to be effective in the treatment of DME. In a study by Arevalo et al., significant improvement in vision and regression in macular edema in 78 eyes given 1-3 IVB within 6 months.[9] Although less IVB injections were administered irregularly, mean CMT was decreased from 387 µm to 275 µm (111.3 µm; 29% thinning). The reason for better results than our study may be due to regression of macular edema on month 6, higher baseline level of edema (479.0 µm) in our study and use of different OCT devices. Authors reported that there was ≥2 order improvement in 55.1%, no change in 41.1% and ≥2 order worsening in 3.8% of cases. In our study, visual improvement was achieved in 86.7% of eyes. Better visual results in our study may be due to completion of three loading doses of bevacizumab without marked delay. Solaiman et al. reported thinning in CMT (150.8 µm; 31.3%) an significant visual gain by IVB in one month; however, significant visual improvement and CMT reduction could be maintained in only IVB plus modified grid group on month 3. Many studies reported different rates for anti-VGEF resistant DME. In our study, 4 cases(13.3%) were unresponsive to IVB injections. In the REACT study[11], IVR was administered with pro re nata regimen in eyes with persistent central DME despite at least 6 (mean: 8.6) during 1-year follow-up, providing significant improvement in vision and reduction in edema. Similar outcomes have been reported in other industry-sponsored studies.[1,11,12]

In the study by Haritaoğlu et al., at least 2 IVB injections (1.25/0.05 mL) were administered 70% of 51 eyes and the patients were followed for 6-12 weeks.[6] All patients had history of previous treatments such as focal or panretinal laser, vitrectomy or intravitreal triamcinolone. In the study, baseline visual acuity was 14.4 ETDRS letters and CMT was 501 µm. There was 124 µm (24.7% reduction in CMT from 501 µm to 377 µm. The reduction in CMT was found to be statistically significant; however, visual improvement did not reach statistical significance. Authors suggested that this may be due to delay in the treatment while receiving other treatment options and insufficient number of injections. Lam et al. conducted a randomized study including 48 eyes in order to establish optimal IVB dose (1.25 mg or 2.5 mg). In the study, three loading doses of monthly IVB were administered and patients were followed for 6 months. A significant improvement in vision and regression in edema were achieved. No difference was found in efficacy between doses evaluated. Authors found that IVB was more effective in treatment-naïve patients.[13] The better visual outcomes may be explained by the fact that only treatment-naïve patients were evaluated in our study.[6,7] In a study from Turkey, Uslu et al. treated 20 eyes with diffuse DME and previous history of treatment with single dose IVB and followed patients for 3 months. Significant improvement was achieved in 75% of the eyes on month 1 while vision remained unchanged in 20% and decreased in 5%. Mean visual acuity showed significant improvement from 0.28 to 0.44. Again, CMT was significantly decreased from 422 µm to 316µm (106 µm; 25%). In the BOLT study[4], There was ≥2 lines visual improvement in 49% and ≥3 order in 32% of the cases with IVB.. In our study, these rates were 56.7% and 30%, respectively. These rates were only 7% and 4% by MLT. These data clearly show that the era of grid laser beginning with ETDRS has ended in central DME by anti-VGEF era. The CMT reduction was 146 µm. This result was achieved by 13 IVB over 2 years, which is better than our results.[4]

In DRCR.net study[3], additional focal laser therapy was performed in 56% of IVB patients upon week 24. Focal laser therapy was performed in mix type DME where diffuse and focal edema exist together. In our study, this rate was 10%. In first year, mean visual gain was 9.7 letters in IVB, 11.2 in IVR and 13.3 in IVA. In the subgroup with baseline visual acuity of 69 ETDRS letters (49.6 letters in our study), visual gain was greater with 11.8 letters in IVB, 14.2 letters in IVR and 18.9 letters in IVA. Given these results, visual gain would be increased by additional injection in remaining 9 months in our cases. Given the cost-benefit rate, it is highly good outcome. Again, in DRCR.net study, mean reduction in CMT was -101 µm by IVB after 12 months. In our study, CMT reduction was -86 µm after 3 months. In the second year outcomes of DRCR.net Protocol T[15], mean visual gain was 10.0 letters in IVB and 12.3 letters in IVR with approximately 15 injections. In eyes with baseline VA<0.4, IVB efficacy was found to be comparable with IVR. In eyes with baseline VA>0.5,

visual gain was limited due to roof effect and IVB efficacy was found to be equal to remaining agents.[3,15]

Regarding safety, no infection or toxic reaction or systemic thromboembolism was observed after IVB in our cases in agreement with literature. However, in some cases, subconjunctival hemorrhage was developed, which was reported as 40% in previous studies.[14] Endophthalmitis was reported by 0.45% (1/224) with IVA and by 0.46% (1/218) with IVR; however, no endophthalmitis was observed after 218 IVB injections which were performed by dose adjustment.[3] The incidence of systemic adverse effects requiring hospitalization was comparable across three agents while any cause mortality rate was reported as 2% in IVB and IVR and 1% in IVA.[3] The incidence of thromboembolic events was 8% in IVB, 12% in IVR and 5% in IVA (p=0.09).[15] It was reported that IOP reached to 34.6 mmHg within first hour after IVB, which was then decreased to 21.9 mmHg on minute 30 and 20.6 mmHg on hour 1 [16]. In our study, no IOP elevation was observed on day 1 after injection.

This study has some limitations including limited sample size and follow-up as short as 3 months. Again, there is no control group and IVB was used in off-label manner. However, in this study, it was only aimed to evaluated efficacy after loading dose but not at long-term. In addition, OCT markers such as DRIL, subretinal fluid or hyper-reflective dots were not addressed. The strength of the study is inclusion of treatment-naïve patients only, allowing assessment of IVB efficacy regardless of previous treatments. The lower rate of laser therapy also supported the study. It is also important that CMT changes and vision were objectively assessed using real-world data after 3 IVB injections in our study. It was found that three loading doses of IVB was effective in 90% of the cases. Injections should be continued until complete regression of macular fluid. When we retrospectively reviewed unresponsive eyes (n=4), it was seen that there was epiretinal membrane and vitreomacular traction which was overlooked in foveal sections and led indirect tangential traction in one case with typical DME at fovea in which vision and CMT remained unchanged. In the cases shown in Figure 2, we think that Telengiectatic Capillary (TelCap), which is newly defined in the literature, was the reason for unresponsiveness. The TelCap with continuous leakage can be seen at left of central exudate as saccular vascularity which was hyper-reflective at periphery and hypo-reflective at center (Figure 2). It has been reported that such giant aneurysms are resistant to anti-VGEF therapy and can be treated by argon laser photocoagulation guided by infrared reflectance imaging.[17] Remaining two eyes exhibited primary unresponsiveness. In such cases another anti-VGEF agent or dexamethasone implant therapy may be considered either after additional 2-3 IVB injections based on expectation of delayed response or directly.[1,11,12]

In conclusion, it can be suggested that 3 consecutive loading doses of Avastin (1.25 mg) is a successful first-line treatment in treatment-naïve central DME cases with baseline VA of 5-35 letters, providing anatomic and visual improvement. IVB injections may be supported by focal laser photocoagulation in cases with focal edema. For safety concerns, postponing injections in cases with active conjunctivitis or blepharitis, avoiding injection in cases

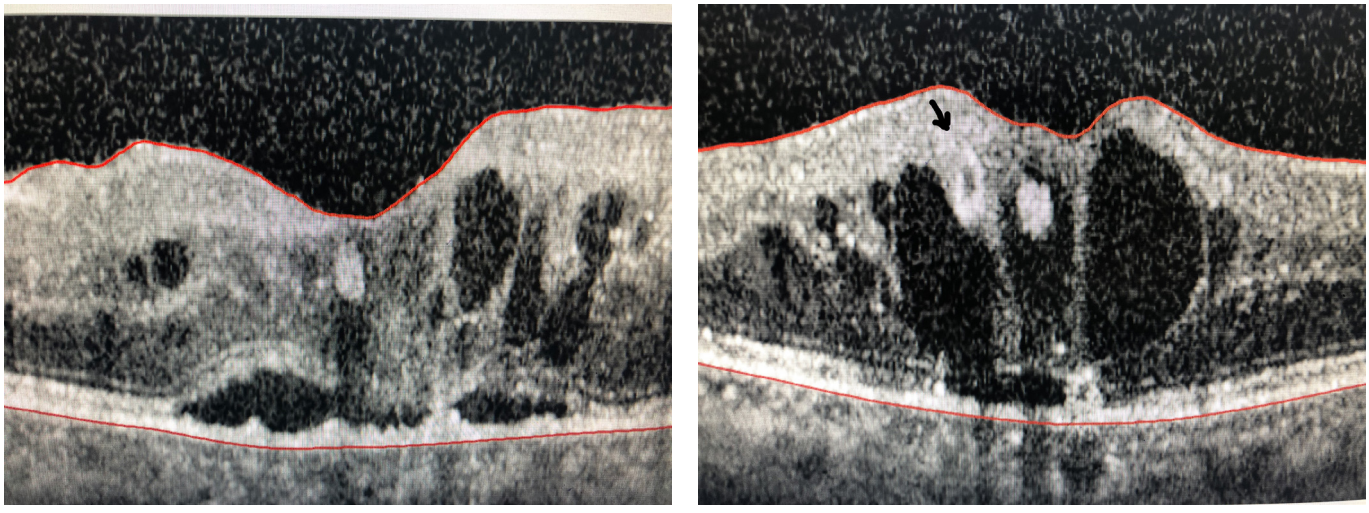


Figure 2: A. *Pretreatment; Intraretinal exudate and cysts and subretinal fluid (SRF). Central macular thickness (CMT); 407µ.* **B.** *After three doses of intravitreal bevacizumab; SRF disappeared; however, intraretinal exudate remained unchanged and degenerative cyst were formed. CMT was further increased ; 485µ. Interrupted ellipsoid zone. Telengiectatic Capillary (TelCap) lesion can be seen at left of central exudate, leading persistent DME.*

with high arterial pressure or history of cardiovascular or cerebrovascular thromboembolic event within prior 6 months will prevent undesired adverse events.

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