

Effect of intravitreal bevacizumab on diabetic macular edema with hard exudates

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Background: We evaluated the efficacy of intravitreal bevacizumab on diabetic macular edema with subfoveal and perifoveal hard exudates.

Materials and methods: Eleven eyes (11 patients) exhibiting diabetic macular edema with subfoveal and perifoveal hard exudates were included in this prospective, nonrandomized interventional pilot study. All patients were treated with monthly scheduled intravitreal bevacizumab injections for 6 months. Changes in the Early Treatment Diabetic Retinopathy Study best corrected visual acuity, amount of hard exudates on fundus photography, and macular edema detected by central subfield thickness on spectral domain optical coherence tomography after six serial injections, were assessed. The amount of hard exudates at each visit was evaluated as pixels in fundus photography, using an Adobe Photoshop program.

Results: Ten of 11 patients completed follow-up. The mean Early Treatment Diabetic Retinopathy Study best corrected visual acuity was 59.9 ± 5.7 letters (Snellen equivalent, 20/63) at baseline evaluation. The best corrected visual acuity exhibited no significant difference at month 6 compared with at baseline (57.9 ± 6.0 letters or 20/70 at month 6; $P=0.085$). At month 6, mean central subfield thickness decreased from 370.4 ± 56.5 to 334.6 ± 65.0 μm ($P=0.009$). The mean amount of hard exudates increased from 4467.1 ± 2736.1 to 6592.4 ± 2498.3 pixels at month 6 ($P=0.022$). No serious adverse events occurred.

Conclusion: Continuous intravitreal bevacizumab was found to have no benefit in visual acuity and amount of hard exudates, despite the improvement of macular edema at 6 months.

Keywords: bevacizumab, diabetic macular edema, hard exudates

Introduction

Diabetic macular edema (DME) is one of the most common causes of visual deterioration in the diabetic population.¹ DME has been subdivided into focal and diffuse types.² Focal macular edema is characterized by focal leakage from microaneurysms and is often associated with hard exudates. The diffuse type of edema is characterized by diffuse leakage from the retinal capillary beds and formation of cystoid spaces. The Early Treatment of Diabetic Retinopathy Study (ETDRS) reported that focal laser treatment to leaking microaneurysms and/or grid treatment to areas of diffuse leakage substantially reduced the risk for visual loss in patients with clinically significant macular edema.³ The ETDRS also revealed that the efficacy of laser treatment was not influenced by the source of leakage (predominantly focal versus intermediate to diffuse), presence of cystoid changes, or severity of hard exudates.⁴ Since that study, focal/grid laser therapy has been the mainstay of treatment for DME. However, laser treatment only prevents further visual deterioration, rather than improving vision. Furthermore, many clinicians believed that a notable number of patients with diffuse DME remained unresponsive to laser photocoagulation,

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whereas patients with focal DME responded well to focal laser photocoagulation.⁵

Vascular endothelial growth factor (VEGF) is overexpressed in diabetic eyes and plays a key role in the development of DME; therefore, anti-VEGF treatment is one of the most promising approaches for the treatment of DME.^{6,7} Results of several recent prospective studies of DME with ranibizumab consistently revealed that ranibizumab monotherapy or ranibizumab combined with laser treatment were superior to laser treatment alone in terms of functional and anatomical outcomes in center-involving clinically significant macular edema.^{8–14} Bevacizumab demonstrated similar efficacy in smaller prospective trials.¹⁵

Results of these studies were consistent across all subgroups of DME patients, including patients with focal or diffuse DME.^{13,14} However, patients with DME make up a heterogeneous group of patients with variable clinical manifestations. Many cases of DME have mixed features of focal and diffuse edema, making a clear distinction difficult. Diabetic Retinopathy Clinical Research Network investigators found that the terms “focal DME” and “diffuse DME” were frequently used without clear definitions.¹⁶ The evaluation of published information regarding the responses of focal and diffuse DME to treatment and the importance of focal and diffuse DME in assessing prognosis is hindered because the terms are used inconsistently. The investigators suggested that more reproducible methods of grading source and patterns of leakage, area of thickening, and quantitation of hard lipid exudates will need to be devised.¹⁶ The best treatment modality or combination of therapeutic modalities for a given patient are yet to be determined.

In this pilot study, we evaluated the efficacy of continuous intravitreal bevacizumab monotherapy in patients exhibiting DME with subfoveal and perifoveal hard exudates at 6 months. In these patients, focal laser treatment was not applicable because some or many of the microaneurysms associated with hard exudates were located within 500 μm of the fovea center.

Methods

This was a prospective, nonrandomized interventional pilot study. The patients were recruited from Retina Service at Seoul St Mary's hospital between June 16, 2011, and May 30, 2012. The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the Seoul Saint Mary's Hospital Institutional Review Board/Ethics Committee before recruitment. All participants signed an informed consent form after a detailed explanation of the

study design, associated investigations for scientific purposes, and adjuvant imaging procedures. The study was registered at www.clinicaltrials.gov under the identifier NCT01422018.

Inclusion criteria were 250 μm or more of central subfield thickness (CST), as measured by spectral domain optical coherence tomography (SD-OCT); fovea-center involving DME; and presence of hard exudates in the perifoveal area, with or without subfoveal involvement. Exclusion criteria were study eyes with any pharmacologic or surgical intervention within 6 months; panretinal or focal/grid laser photocoagulation within 6 months, history of ocular diseases other than diabetic retinopathy, ischemic maculopathy, massive subfoveal hard exudates or subretinal fibrosis, media opacity, pharmacologic intervention on the fellow eye within 3 months, or thromboembolic event within 6 months.

Patients received six consecutive monthly injections of bevacizumab (Avastin[®]; Genentech, Inc., South San Francisco, CA, USA; 1.25 mg in 0.05 mL). A comprehensive ocular examination including ETDRS best corrected visual acuity (BCVA) testing, slit-lamp examination, color fundus photography, macular cube 512 \times 128 scan by SD-OCT, and fluorescein angiography were evaluated as a baseline examination. Follow-up examinations, including ETDRS BCVA and slit-lamp examination, were conducted at every monthly visit, whereas color fundus photography and SD-OCT were conducted at 2-month intervals. BCVA was measured at 4 m with standard ETDRS protocols, using a testing chart transilluminator (Lighthouse International, New York, NY, USA). Visual acuity was scored as the total number of letters read correctly.

The amount of hard exudates was measured using color fundus photography (Topcon Corporation, Tokyo, Japan) and Photoshop (Photoshop 5.5; Adobe Systems Inc., San Jose, CA, USA), as Smith et al¹⁷ previously described, with a few modifications. The fundus images were saved as 24 bit RGB TIFF files, with 256 levels of intensity value for each color channel. The images had minimum resolutions of 2,700 pixels/inch. To achieve a consistent size of each image from a patient, the sizes of the images were adjusted so that the diameter of the optic disc of each image was the same. The amount of hard exudates was determined by the magic wand tool (with adjustment of tolerance of 1 to 5, brush size 5, and zoom to 200%) by the authors. The selected area was measured in pixels (three times for each author), and the average values were taken for the statistical analysis (Figure 1). The amount of hard exudates within 500 μm was also evaluated by the same technique. A concentric circle centered on the fovea with a diameter of 500 μm was made using the built-in

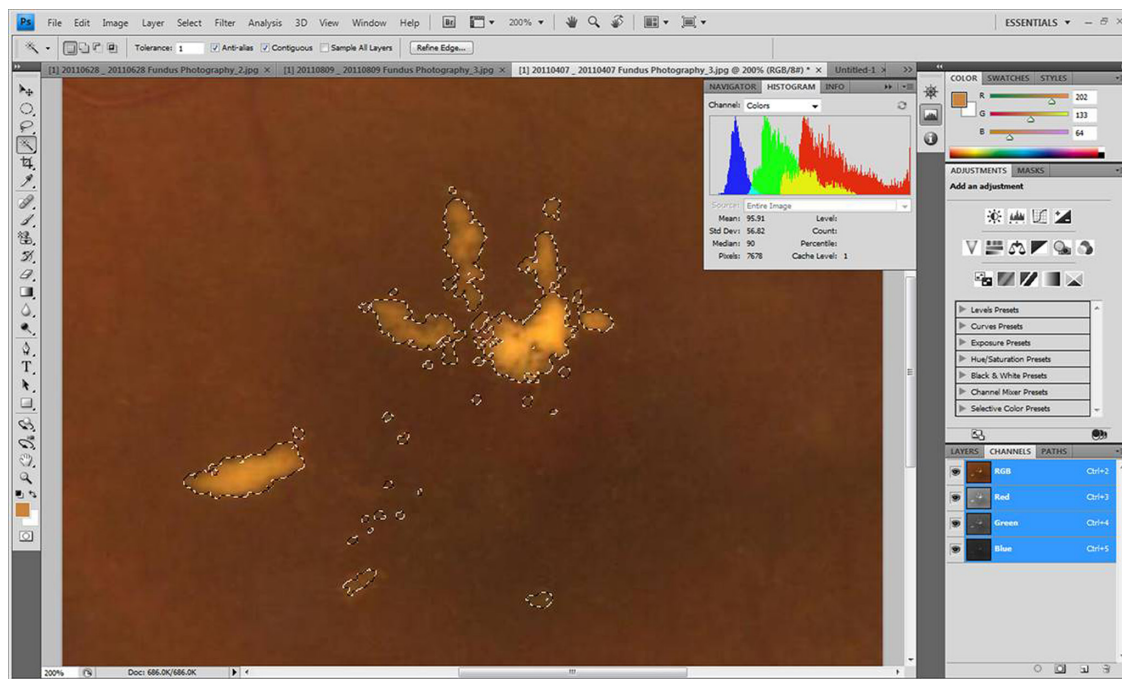


Figure 1 Measuring the amount of hard exudates with color fundus photography and the Photoshop program (Photoshop 5.5; Adobe Systems Inc, San Jose, CA, USA). **Notes:** The selected area by the magic wand tool (with adjustment of tolerance of 1–5, brush size 10, and zoom to 200%) is expressed in pixels by the histogram option.

caliper tool in the fundus photography instrument, and the amount of hard exudates within the circle was measured.

The SD-OCT was performed with the Cirrus HD-OCT system (software version 3.0, Carl Zeiss Meditec AG, Jena, Germany), according to macular cube 512×128 protocol. The standardized macular cube protocol consisted of 512 horizontal A-scans and 128 vertical B-scan lines with an acquisition time of 2.4 seconds at 6 mm square centered on the fovea. The CST calculated from built-in software was used for statistical analysis.

The serum level of total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, and glycated hemoglobin level were measured at the initial and final visits.

Statistical analysis was conducted using SPSS (version 12 for Windows; SPSS Inc., Chicago, IL, USA). The Wilcoxon signed-rank test was used to compare the differences between initial and final BCVA, amount of hard exudates, CST, and lipid profiles. Inter- and intraexaminer measuring consistency was determined by having both examiners measure the same image repetitively (ten times each). The bias for each measurement was calculated by the mean difference in data between measurement and examiners; the paired *t*-test determined whether levels of bias were significantly different from zero, as previously described.¹⁸ The limits of agreement, encompassing 95%

of differences between two measurements (mean ± [1.96× standard deviation]), were established using the standard deviation of differences.

Results

Eleven eyes were enrolled in this prospective interventional study. The data from ten patients were analyzed because one patient was not present for regular follow-up after the second injection. Baseline characteristics of the enrolled patients are described in Table 1. There were six female and four male patients, with a mean age of 62.9±6.7 years. They were diagnosed with and treated for type 2 diabetes for a mean of 15.3±9.6 years. The stages of diabetic retinopathy were moderate nonproliferative diabetic retinopathy in three eyes, severe nonproliferative diabetic retinopathy in six eyes, and proliferative diabetic retinopathy in one eye. Five patients had been diagnosed with hypertension and were taking oral hypotensive drugs. Nine patients were taking lipid-lowering drugs for hyperlipidemia. At baseline, glycated hemoglobin, triglyceride, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol levels were 7.1%±0.6% and 245.1±40.6, 208.4±26.1, 49.0±6.6, and 116.8±25.5 mg/dL, respectively (normal ranges are 4.4%–6.0% and 40–200, <200, >60, and <100 mg/dL, respectively). At month 6, no patient was found to exhibit changes in serum lipid and glycated hemoglobin levels more

Table 1 Clinical and laboratory characteristics of enrolled patients

Number	Sex	Age, years	Duration of diabetes, years	Stage of DMR	Previous treatment	HBP	Lipid-lowering drugs	ETDRS BCVA, letters		CST, μm		Hard exudates, pixels		Hard exudates $\leq 500 \mu\text{m}$ from fovea, pixels	
								Month 0	Month 6	Month 0	Month 6	Month 0	Month 6	Month 0	Month 6
1	F	67	15	Moderate NPDR	FRP, 2 years ago	No	Yes	62	53	384	355	7206.2	11121.0	92.5	157.8
2	F	56	10	Severe NPDR	PRP, 2 years ago; FRP, 2 years ago	No	Yes	50	48	305	213	2695.3	4523.2	686.0	407.5
3	M	70	8	Moderate NPDR	No	Yes	Yes	58	55	483	473	2413.5	3726.0	74.2	446.9
4	F	63	18	Moderate NPDR	PRP, 1 year ago	No	Yes	68	68	369	342	848.3	2577.7	531.3	560.7
5	F	59	2	Severe NPDR	PRP, 5 years ago	No	No	62	58	420	332	3188.7	7375.8	171.2	742.0
6	F	52	8	Severe NPDR	No	Yes	Yes	65	62	297	312	7647.2	7954.3	651.7	877.3
7	M	75	30	Severe NPDR	PRP, 2 years ago	Yes	Yes	57	53	354	302	6375.8	7645.2	322.8	880.2
8	M	62	10	PDR	PRP, 2 years ago; FRP, 1 year ago	No	Yes	56	54	379	347	844.0	8070.5	31.9	930.7
9	M	64	24	Severe NPDR	FRP, 2 years ago	Yes	Yes	66	64	321	304	6134.2	7257.9	307.2	1033.3
10	F	61	5	Severe NPDR	PRP, 7 years ago	Yes	Yes	55	62	402	366	7317.8	5672.0	360.5	2127.3

Abbreviations: DMR, diabetic retinopathy; HBP, hypertension; ETDRS, Early Treatment of Diabetic Retinopathy Study; BCVA, best-corrected visual acuity; CST, central subfield thickness; F, female; NPDR, nonproliferative diabetic retinopathy; FRP, focal laser photocoagulation; PRP, panretinal photocoagulation; M, male; PDR, proliferative retinopathy.

than 20% compared with baseline levels ($6.9\% \pm 0.5\%$ and 247.4 ± 37.5 , 210.6 ± 20.7 , 47.6 ± 6.4 , and 118.0 ± 25.1 mg/dL, respectively).

Figure 2 presents the treatment outcomes, changes of ETDRS BCVA, CST, and the amount of hard exudates. The mean ETDRS BCVA was 59.9 ± 5.7 letters (Snellen equivalent of 20/63) at baseline and 57.9 ± 6.0 letters (Snellen equivalent of 20/70) at month 6 ($P=0.085$; Figure 2A). There was no significant difference between the mean values at baseline and each follow-up. Eight patients lost 1–9 ETDRS letters at month 6. One patient was found to have the same ETDRS visual acuity, and another patient gained seven ETDRS letters at month 6.

The mean CST was 370.4 ± 56.5 μm at baseline and improved to 356.6 ± 51.9 μm at month 2 ($P=0.041$). The CST improved in proportion to repeated injections; as a consequence, CST was 334.6 ± 65.0 μm at month 6 ($P=0.009$; Figure 2B).

No statistically significant bias was evident with respect to interexaminer and intraexaminer measurements on the amount of hard exudates (Table 2). The mean amount of

hard exudates was 4467.1 ± 2736.1 pixels at baseline, but it increased to 6592.4 ± 2498.3 pixels at month 6 ($P=0.022$; Figure 2C). Only one patient was found to have decreased hard exudates at more than 20% of baseline at month 6; however, five patients were found to have an increase in hard exudates at more than 20% of baseline at month 6.

Hard exudates were present within 500 μm from the fovea center in every enrolled eye. The mean amount of hard exudates within 500 μm from the fovea center also exhibited a statistically significant increase, from 322.9 ± 237.5 pixels at baseline to 807.3 ± 536.6 pixels at month 6 ($P=0.017$). Figure 3 shows the changes in hard exudates of a selected patient. No significant ocular or systemic complications were reported during the follow-up period.

Discussion

In the present study, intravitreal bevacizumab monotherapy had no beneficial effect in DME with subfoveal and peri-foveal hard exudates in terms of visual acuity and amount of hard exudates at 6 months of follow-up. Despite a significant reduction of CST, only one of ten eyes showed

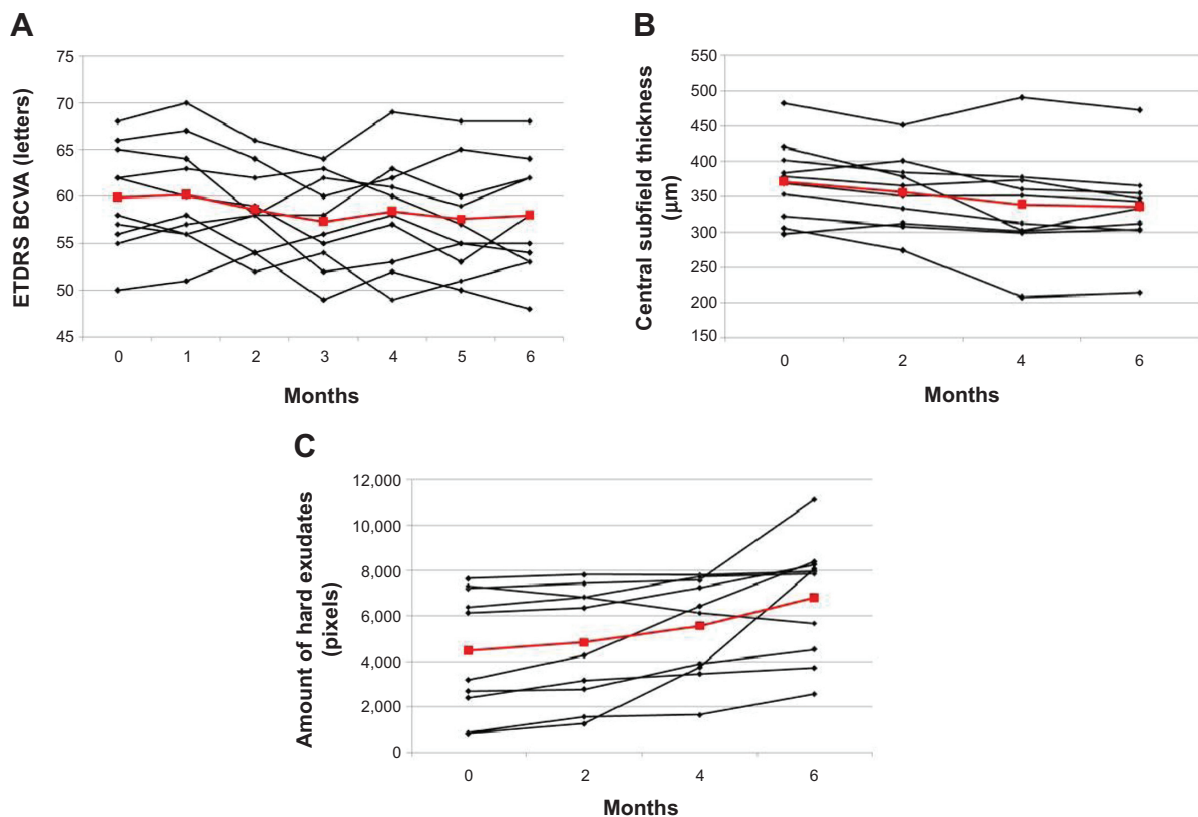


Figure 2 Clinical results of enrolled patients from month 0–6 (mean depicted in black).

Notes: Mean \pm standard deviation (range). (A) Best corrected visual acuity (BCVA) as Early Treatment of Diabetic Retinopathy Study (ETDRS) letters. (B) Central subfield thickness (μm) detected by Cirrus HD-OCT system (software version 3.0, Carl Zeiss Meditec AG, Jena, Germany), according to macular cube 512 \times 128 protocol. (C) Changes in amount of hard exudates (in pixels) detected by fundus photography and the Photoshop program (Photoshop 5.5; Adobe Systems Inc, San Jose, CA, USA).

Table 2 Repeatability for the interexaminer and intraexaminer measurements

Measurement	Mean difference	Standard deviation of the differences	95% limits of agreement
Interexaminer comparisons	68.3	218.3	-357.6, +496.2
Intraexaminer comparisons	32.9	210.5	-379.8, +445.6

improved visual acuity after six serial injections. It is notable that visual outcome in this study is different from that of previous studies.⁸⁻¹⁵ The benefits of ranibizumab were observed as early as 7 days after treatment initiation, signifying a very rapid effect of the drug in DME.¹⁴ Over the same time frame of 6 months, the mean gain of visual acuity was 7.24 letters in the ranibizumab group in the Ranibizumab for Edema of the Macula in Diabetes 2 study, despite less-aggressive dosing consisting of four injections.¹¹ In addition, most studies reported favorable visual outcomes regardless of injection schedule; they noted six or more letter improvements in the ranibizumab group at month 6.⁸⁻¹⁴

Retinal hard exudates consist of lipids and lipoproteins that leak from microaneurysms and dilated capillary segments. Subsequent to laser treatment, hard exudates tend to enlarge and shift centrally with the resolution of

macular edema and may decrease after a certain period.^{20,21} This indicates that precipitation of lipid was induced by the resorption of water and consequent concentration of poorly soluble and poorly diffusible lipids. Our current study shows that the changes in the extent and distribution of hard exudates after continuous intravitreal bevacizumab injections were similar at 6 months. Although the action mechanisms are different, laser and anti-VEGF treatment have a concomitant feature, which has a role in reducing vascular leakage. Anti-VEGF treatment does not have the additional benefit of facilitating resorption of lipid or proteinaceous materials. However, it is possible that reduction of hard exudates and visual improvement might have occurred in our cases at a longer time interval with or without further injections. Nevertheless, our results provide valuable information that has an important clinical implication. Hard exudates are associated with both photoreceptor degeneration and degeneration of neuronal elements in the outer plexiform layer. An increasing amount of hard exudates is independently associated with an increased risk for visual impairment. Rapid resorption of hard exudates as well as intraretinal and subretinal fluid is a desirable endpoint of macular edema treatment.

Several studies have consistently demonstrated that intravitreal triamcinolone resulted in rapid reduction of hard exudates and improvement of visual acuity.²²⁻²⁵ Extravasated

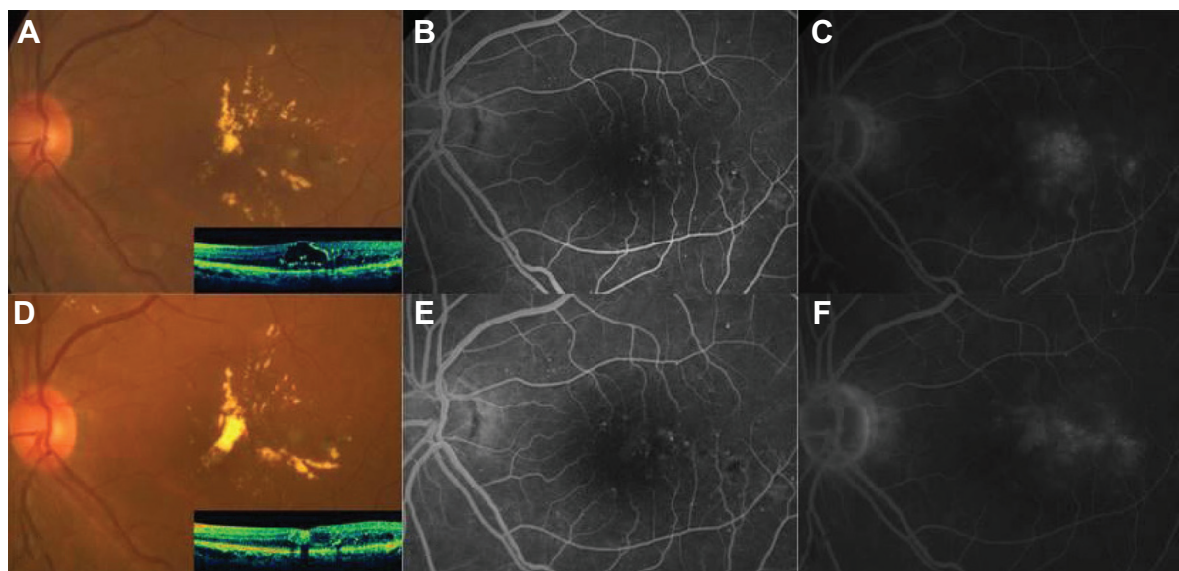


Figure 3 Color fundus photography, optical coherence tomography, and fluorescein angiography at baseline and final follow-up visit of a 67-year-old woman with diabetic macular edema associated with hard exudates treated with six serial injections of intravitreal bevacizumab.

Notes: The patient was diagnosed as having type 2 diabetes 15 years ago and was taking oral hypoglycemic and lipid-lowering drugs. She had a history of focal laser photocoagulation for leaking microaneurysms 2 years ago. (A) Diabetic macular edema associated with subfoveal and perifoveal hard exudates (7206.2 pixels) were detected on optical coherence tomography at baseline. The patient's best-corrected visual acuity was 20/63. (B) Early-phase and (C) late-phase fluorescein angiography showed multiple leaking microaneurysms in the subfoveal and perifoveal area at baseline. (D) After six serial injections, hard exudates were increased (11121.0 pixels), whereas macula edema was reduced on optical coherence tomography. (E) Early-phase and (F) late-phase fluorescein angiography showed decreased leakage from microaneurysms after six serial injections. The patient's best corrected visual acuity was 20/100 at final visit.

lipid materials induce characteristic inflammatory response with involvement of multiple cell types and further accumulation of lipids.^{26–30} Triamcinolone may have advantages for the resolution of hard exudates by not only stabilizing the blood–retinal barrier^{31–35} but also exhibiting an anti-inflammatory action that may result in the inhibition of proinflammatory macrophages and leukocytes, prevention of extracellular matrix remodeling,^{36,37} and inducing differentiation of specific anti-inflammatory macrophages, which have a high capacity for phagocytosis of proinflammatory stimuli such as lipids.^{37,38} For patients with this type of DME, adding triamcinolone adjunctively to anti-VEGF approach, at least in the initial treatment, may have the benefit of rapid removal of hard exudates.

Elevated serum lipid levels are associated with an increased risk for hard exudates.³⁹ In the present study, nine of ten patients exhibited slightly higher lipid profiles at their initial and final visits, despite lipid-lowering medication and diet control. Tighter lipid control might result in more favorable outcomes regarding the amount of hard exudates in these patients.

The present study showed that after 6 months, there was no beneficial effect of intravitreal bevacizumab for DME with subfoveal and perifoveal hard exudates in terms of visual acuity. Hard exudates increased in extent and tended to move to the foveal side, despite continuous injections. In addition to the short study period, the small number of enrolled patients is another limitation of this study. Further studies with a larger sample size and longer follow-up are required to confirm our study results as well as compare the efficacy of each and combined treatment modalities for this pattern of DME.

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Disclosure

The authors report no conflicts of interest in this work.

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