RESEARCH ARTICLE

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DOES BASELINE SUB-FOVEAL CHORIODAL THICKNESS DETERMINES TREATMENT RESPONSE TO INTRAVITREAL AFLIBERCEPT IN DIABETIC MACULAR EDEMA?

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Abstract

Introduction: To determine the predictive value of baseline SFCT for response to treatment with serial intravitreal aflibercept injections for diabetic macular edema (DME).

Methods: A prospective multi-center study was done. Eyes with DME (n=95) were treated with intravitreal aflibercept injections q4week for first 5 doses, followed by 2mgq8week, respectively. SFCT and central macular thickness (CMT) were measured with serial enhanced depth imaging optical coherence tomography scans done at baseline and after the last injection. A functional responder was one with >5 ETDRS letter gain in vision. An anatomical responder was one with SFCT reduction>25u.

Results: At 6 months, after the last IV injection of aflibercept, the mean SFCT decreased significantly (319±47 at baseline, 250±36 at 6 months, P<0.001). A significantly higher baseline SFCT was seen in functional responders as compared to non-responders (329±50 versus 303±36u, independent t-test, P=0.002). Likewise, anatomical responders has a significantly higher baseline SFCT as compared to non-responders (327±51 versus 305±33, P=0.002). Multiple logistic regression (after adjusting for confounders like age, gender, duration of diabetes, and glycemic control, respectively) revealed that higher SFCT had increased odds of having a better functional (odds ratio=1.40, P=0.050) and anatomical outcome (odds ratio=1.23, P=0.001), respectively. The mean vision gain in functional responders and non-responders was 11and 5 ETDRS letters, respectively (P<0.001). The mean vision gain in anatomic responders and non-responders was 10 and 6 ETDRS letters, respectively (P<0.001).

Conclusion: SFCT at baseline predicts response to intravitreal aflibercept therapy in DME patients after adjusting for confounders. Eyes with a thicker baseline sub-foveal choroidal thickness had better anatomic and functional response at 9 months.

Keywords: Diabetic macular edema, aflibercept, sub-foveal choroidal thickness.

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INTRODUCTION

In patients with long standing diabetes, macular edema (DME) is the major cause of reduction in vision and is indicative of a compromised blood retinal barrier; it is often accompanied by changes in the underlying choroidal vasculature. [1]

A study from western India reported that the prevalence of DME was 8.9% and that of referable DME was 2.4%. [2] According to recent estimates, there are 77 million diabetics in India; considering a conservative estimate of 2% diabetics having DME, likely magnitude of treatable DME is 15,40,000 persons. [3] However, the prevalence of DME is likely to increase along with the increasing prevalence of diabetes mellitus, particularly in view of the current epidemics of type 2 diabetes in India. [4]

The choroidal vasculature plays an important role in preservation of visual function by delivering nutrients and removal of metabolic wastes from the outer retinal layers. [5] Diabetic retinopathy is essentially an ischemic retinopathy, leading to hypoxia and consequently overproduction of vascular endothelial growth factors (VEGFs) and other angiogenic factors. This in turn leads to leakage from choriocapillaris; intraretinal fluid accumulation in DME results in reduction of vision; without definitive treatment, DME may lead to permanent vision loss. [6-7]

Now, the standard treatment protocol for DME has transited from laser photocoagulation to intravitreal injections of anti-VEGFs like aflibercept, and ranibizumab, and off-label bevacizumab. Aflibercept has a longer duration of action than ranibizumab and bevacizumab. This implies less frequent dosing with substantial saving in cost of treatment which may be of paramount importance in developing countries like India. [8]

A study by Lains et al found that eyes treated with anti-VEGFs had a significant reduction in sub-foveal choroidal thickness compared to laser treated fellow eye in patients with DME. [9]

A study by Querques et al found that sub-foveal choroidal thickness was significantly reduced in diabetics (indicating thinning) compared with healthy controls using enhanced depth optical coherence tomography imaging (EDI-OCT). [10] Undoubtedly, EDI-OCT imaging has made possible better visualization of the choroidal vasculature and more detailed differentiation of pathological conditions in retina. [11]

Mounting evidence now points towards alterations of choroidal vasculature in DME; whether the baseline sub-foveal choroidal thickness has any predictive value for subsequent response to intervention needs further evaluation.

There is limited availability of data on the effect of aflibercept for the management of DME in the real-world setting. A search of major databases including Pubmed did not reveal any study conducted in the

subcontinent evaluating changes in SFCT following intravitreal aflibercept therapy. In this study, we evaluated the response of intravitreal aflibercept on sub-foveal choroidal thickness and the association between baseline sub-foveal choroidal thickness in previously untreated eyes with DME and the long-term (>9months) response to intervention.

METHODS

Study design: This was a prospective multi-center study carried out at four tertiary care teaching hospitals in the northern part of the subcontinent from July 2021 to June 2022. The trial was approved by the institutional ethics committee. A written informed consent was obtained from all participating patients based on the tenets of the declaration of Helsinki. The trial was registered with UMIN clinical trial registry with registration number UMIN000051561.

Study participants

Inclusion criteria

Study participants comprised of patients who were treatment naive prior to their first aflibercept injection and had center involving clinically significant macular edema in accordance with the Early Treatment Diabetic Retinopathy Study. [12] Patients with a baseline central macular thickness (CMT) of > 250 µm and BCVA between 6/12 (ETDRS letters 70) and 5/60 (ETDRS letters 40) were prerequisites for inclusion. Those patients who received three consecutive aflibercept injections at monthly intervals were included in the study. If both eyes were involved, one eye was selected at random for study inclusion.

A functional responder was defined as one with >5 ETDRS letter improvement in vision. An anatomical responder was defined as one with SFCT reduction>25u after the third loading dose.

Exclusion criteria

Patients with proliferative diabetic retinopathy, prior intravitreal injections of anti-VEGFs or laser photocoagulation, pars plana vitrectomy, age-related macular degeneration, venous occlusion, ocular trauma, pregnancy, and ocular surgery (except cataract surgery) were excluded. Patients with less than 6 months follow-up after the 3rd injection were excluded.

Data collected included demography, duration of diabetes, baseline, and follow-up best-corrected Snellen visual acuity (converted to ETDRS letters), and follow-up duration.

Intervention

For study purpose, all eligible patients received the standard aflibercept therapy (2mg/0.05 ml) administered by intravitreal injection q4Week for first 5 doses, followed by 2mgq8week. Injection of intravitreal aflibercept was administered in the operating room using topical anesthesia with lidocaine eye drops under strict aseptic conditions. After topical anesthesia, the ocular surface was disinfected with povidone-iodine solution. The procedure was carried out using a 30-gauge needle inserted 3.5 mm posterior to the limbus.

The injection site was compressed by cotton swab and the fundus was examined to rule out any complication related to the procedure.

Imaging and BCVA recording.

Spectralis EDI-OCT (Heidelberg Engineering, Heidelberg, Germany), and SD OCT were performed at baseline, after the third loading dose and thereafter at 3 months intervals, with a total of 6 visits (visit 1 at baseline, visit 2 after the third loading dose, visit 3 at 3months after third loading dose, visits 4,5, and at 3 months interval thereafter). At each visit, a complete ophthalmologic examination was done, which included slit lamp examination, recording of best corrected visual acuity using an ETDRS optotype at 2 m distance from the observer, funduscopy, and measurements of SFCT.

Automated CMT measurements were generated using a 25-line raster-scan pattern protocol and SFCT was measured manually as the distance between the RPE hyperreflective line and the chorio-scleral interface. All scans were performed by one expert at each center and was masked to the clinical data of the patient. Glycosylated haemoglobin (HbA1c) levels were measured at baseline and at 6 and 12 months.

Outcome measures

The mean change from baseline in SFCT after last loading dose of Aflibercept was the primary outcome measure. The mean changes in BCVA (ETDRS letters) from baseline to the final study visit were the secondary outcomes of the study.**Sample size calculation**

The sample size was calculated using the online sample size calculator of the university of British Columbia, which can be accessed using the link [https://www.stat.ubc.ca/~rollin/stats/ssize/n1.html.] Sample size calculation was based on the principal of "Inference for a mean, comparing a mean to know a value.' To calculate the sample size, a pilot study was done on 10 patients. The mean baseline SFCT was 296u and after the third injection was 278u. The standard deviation was 62. Considering 80% power (alpha = 0.05), and a precision error of 5% to detect difference of 20% or more in SFCT, the estimated sample size was calculated to be 94.

Statistics

Statistical analysis was performed using IBM statistical software, SPSS Statistics version 29 (IBM Inc.). Data was checked for normality using Shapiro-Wilk test. Outliers were identified by visual inspection of boxplots. Descriptive measures, such as mean with standard deviation (SD), were calculated for all continuous variables, whereas frequencies and percentages were calculated for all categorical variables. The independent-samples t-test was used to determine if a difference exists between the means of two independent groups on a continuous dependent variable. Association between two categorical variable was evaluated using Chi-square tests. A one-way ANOVA was run to determine whether there are any statistically

significant differences between the means of two or more independent groups. A Pearson's product-moment correlation was run to assess the relationship between mean change in CFT and SFCT after intervention. Preliminary analyses showed the relationship to be linear with both variables normally distributed, as assessed by Shapiro-Wilk's test (p > .05), and there were no outliers. A multivariate logistic regression model was constructed to see the impact of baseline sub-foveal choroidal thickness on outcome to intervention (anatomic and functional outcomes), after adjusting for confounders (age, gender, duration of diabetes, and glycemic control, respectively).

BCVA was recorded using Snellen's visual acuity score and was converted to early treatment diabetic retinopathy study (ETDRS) letter scores using the formula ETDRS=85+ [50×log10(Snellen acuity fraction)]. [13] The values used for assessing change were the means of values obtained during the 6-month and 9-month visits; if a value from only one of these visits was available, that value was used.

RESULTS

In this study, 114 eyes of 86 patients with center involving DME had intravitreal injection. Although all patients were compliant with the interventional therapy, 10 patients were lost to follow up after the third injection and were excluded from the study. The socio-demographic and clinical data of patients (n=104) is mentioned in Table 1.

Table 1. Sociodemographic and clinical characteristics. *HbA1c (Glycosylated haemoglobin), ETDRS (Early treatment diabetic retinopathy study), BCVA (best corrected visual acuity), Log MAR (logarithm of the minimum angle of resolution), SFCT (Sub-foveal choroidal thickness).

Parameter	Value
Age (Mean± standard deviation)	60.6±6.2
Gender (N, %)	
Male	60(57.7)
Female	44(42.3)
HbA1c (Mean± standard deviation)	8.5±1
Fasting Blood Sugar (Mean± standard deviation)	142.8±36.4
Duration of diabetes (years)	12.2±1.6
ETDRS vision baseline	52.4±19.7
Baseline BCVA (Log MAR)	0.64±0.4
Follow up after 3rd IV injection (months)	12.4±3.4
Anatomical Responders (SFCT change >25u)	65(62.5)
Functional responders (ETDRS improvement >5Letters)	62(59.6)

Comparison of outcome measures in responders and non-responders

Functional outcome

Table 2 compares functional outcome measures between responders and non-responders. At 6 months after the third IV injection of aflibercept, the mean SFCT decreased significantly (319±47 at baseline, 250±36 at 6 months, P<0.001). The baseline SFCT in functional responders was significantly higher (independent t-test, P=0.002) as compared to non-responders (329±50 versus 303±36u, respectively). A paradoxical increase in SFCT was seen at 9 months. Figure 1a compares the mean change in SFCT between non-responders and responders by functional response. The mean vision gain in functional responders and non-responders was 11and 5 ETDRS letters, respectively (P<0.001). Figure 2a compares ETDRS vision in functional responders.

Table 2. Outcome measures by functional outcome SFCT (Sub-foveal choroidal thickness), CMT (central macular thickness), (ETDRS gain >5 letters).

Parameter	Non-responder (ETDRS gain<5 letters)	Responder (ETDRS gain>5Letters)	P value
SFCT (u)			
Baseline	303±36	329±50	0.002
SFCT 3M	284.6±31.3	263±35.4	0.002
SFCT6M	259±35.8	244.7±34.9	0.047
SFCT 9M	288.7±32.6	270±36.1	0.009
CMT			
Baseline	430±141.5	378.5±103.4	0.033
3M	353±78	314±77	0.014
6M	332±79.1	283±62	0.001
9M	362±75	323±79	0.013
ETDRS vision			
Baseline	53±27.1	62±11.4	0.001
3M	53.7±27.3	70.5±10.4	0.001
6M	58.5±29.5	76.5±10.4	0.001
9M	54.1±27.4	71.8±3.2	0.001

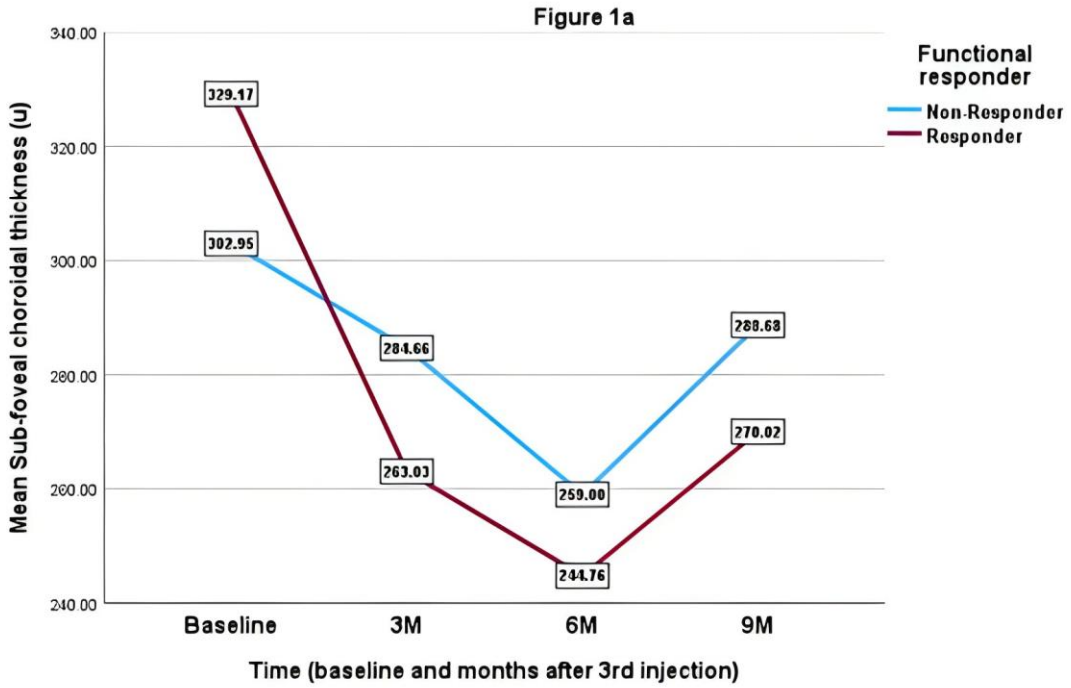

Figure 1a. A line diagram showing changes in sub-foveal choroidal between functional responders and non-responders.

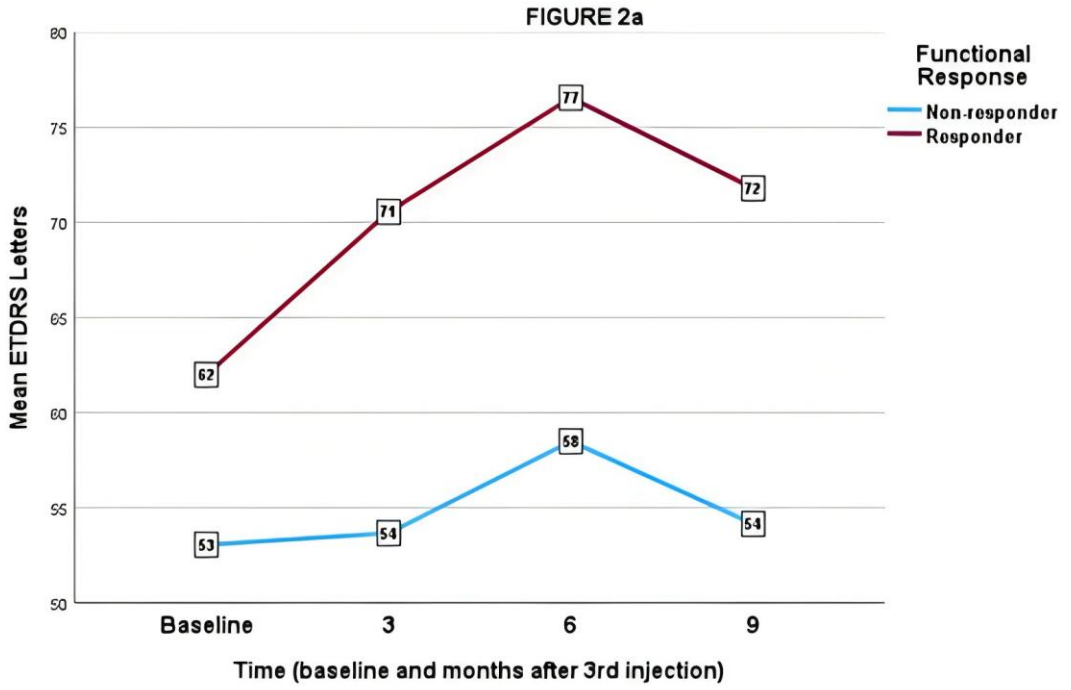

Figure 2a. A line diagram showing changes in ETDRS vision between functional responders and non-responders.

Anatomical outcome

Table 3 compares outcome measures by anatomical outcome (SFCT change >25u). The mean baseline SFCT in responders was significantly higher (independent t-test, P=0.002) as compared to non-responders (327±51versus 304.5±33, respectively).

Table 3. Outcome measures by anatomical outcome (SFCT reduction>25u)

Parameter	Non-responder (SFCT reduction<25u)	Responder (SFCT reduction>25u)	P value
SFCT (u)			
Baseline	304.5±33	327±51	0.002
SFCT 3M	286±31	262±35	0.001
SFCT6M	260±27	255±39	0.014
SFCT 9M	291±34	268±34	0.001
CMT (u)			
Baseline	404±152	396±100	0.807
3M	349±73	317±81	0.050
6M	317±80	293±67	0.027
9M	355±77	328±79	0.047
ETDRS vision			
Baseline	54±24.4	61.2±15.4	0.070
3M	54.9±25	69.5±14.7	0.001
6M	60±27	75.3±15.6	0.001
9M	55.4±25.2	70.7±14.8	0.001

A paradoxical increase in SFCT was seen at 9 months. The mean SFCT increased by 36.5±26u. Figure 1b compares the mean change in SFCT between non-responders and responders by anatomical response.

The mean vision gain in anatomic responders and non-responders was 10 and 6 ETDRS letters, respectively (P<0.001). Figure 2b compares ETDRS vision between anatomical responders and non-responders.

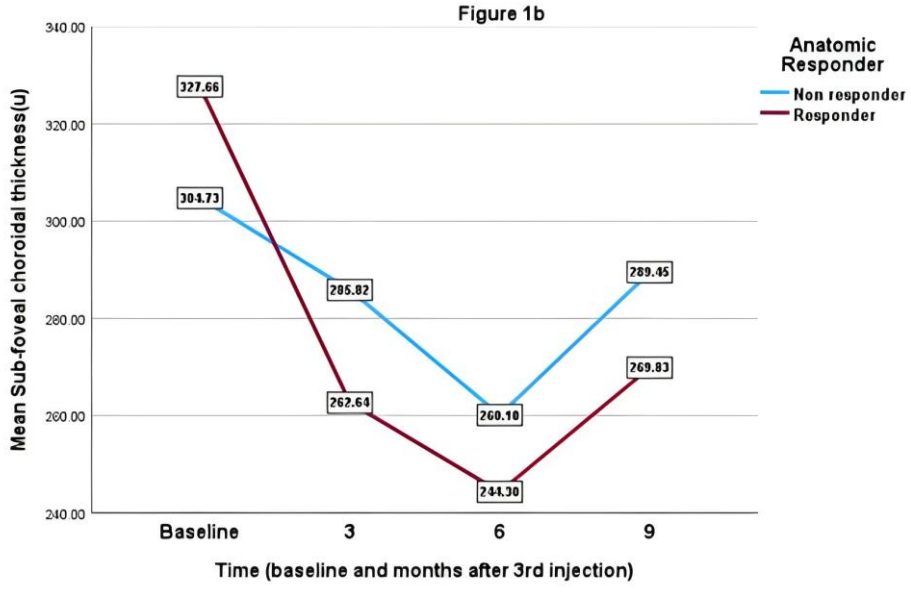

Figure 1b. A line diagram showing changes in sub-foveal choroidal between anatomical responders and non-responders.

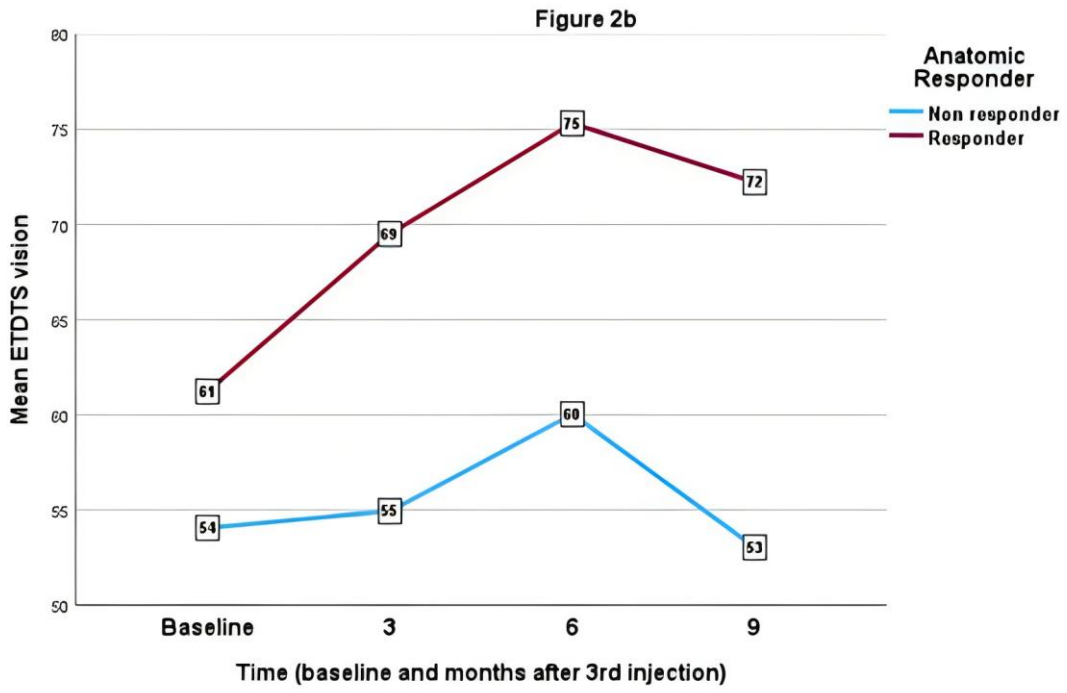

Figure 2b. a line diagram showing changes in ETDRS vision between anatomic responders and non-responders.

Predictors of response to Aflibercept treatment

On multiple logistic regression to ascertain the effects of age, gender, duration of diabetes, SFCT, CMT, BCVA, on the likelihood of patients having good function and anatomical outcome, multivariate logistic regression model was statistically significant, $\chi^2(5) = 11.274$, $P < 0.046$. The model explained 73.0% (Nagelkerke R^2) of the variance in SFCT and correctly classified 78.0% of cases.

A higher baseline sub-foveal choroidal thickness or a worse baseline BCVA were predictors for achieving better functional response after adjusting for age, gender, and duration of diabetes. A higher baseline SFCT had increased likelihood of achieving a better functional outcome (Odds ratio=1.21, 95%CI 1.04-1.310, P<0.05). Table 4 mentions regressions coefficients for functional outcome.

A higher baseline sub-foveal choroidal thickness and central macular thickness were predictors for achieving better anatomical outcome after adjusting for age, gender, and duration of diabetes. A higher baseline SFCT had increased likelihood of achieving a better anatomical response (Odds ratio=1.18, 95%CI 1.0-1.28, P=0.04). A higher baseline CMT had increased likelihood of achieving a better anatomical response (Odds ratio=1.24, 95%CI 1.10-1.341, P=0.001). Table 5 mentions regression coefficients for anatomical outcome.

Table 5. Regression coefficients for anatomical response (after adjustment).

Variable	B (constant)	SE	df	P value	OR	95%CI	
Age	0.008	0.028	1	0.783	1.008	0.954	1.065
Gender	-0.128	0.078	1	0.780	0.880	0.357	2.167
HbA1c	-0.042	0.202	1	0.837	0.959	0.646	1.425
Duration of diabetes	-0.115	0.131	1	0.380	0.891	0.689	1.153
Baseline BCVA	0.026	0.013	1	0.282	1.080	0.995	1.116
Baseline SFCT	0.016	0.005	1	0.056	1.20	1.016	1.280
Baseline CMT	0.001	0.002	1	0.113	1.240	1.100	1.341

Variable(s) entered on step 1: Baseline ETDRS, Baseline SFCT, and baseline CMT.

In this multicenter clinical trial of intravitreal aflibercept therapy for treatment of DME, there was a significant ($P<0.05$) gain in ETDRS letters, reduction in SFCT and CMT at 6 months after the last injection; this was followed by slight but non-significant increase in SFCT and CMT after 9-months follow-up (paradoxical response). The mean decrease in SFCT at 6 months was 73u and the paradoxical rise at 9 months was 27u, respectively. The response in vision was paralleled by the SFCT measurements showing similar proportions of reductions and increases over time. Adverse events related to intravitreal aflibercept were not recorded.

Multiple logistic regression (after adjusting for confounders) revealed that patients with a higher baseline SFCT had increased odds of achieving a better functional (OR=1.4) and anatomic outcome (OR=1.2) after adjusting for confounders (age, gender, duration of diabetes, and glycemic control, respectively). The probable explanation of this observation could be that the choriocapillaris in patients having a greater sub-foveal choroidal thickness at baseline may be thicker and more resistant, better preserving photoreceptor function and a less ischemic retina as compared to patients with a thinner choroid. This may partly explain for the better gain in ETDRS letters in these sub-set of patients.

In our study, the overall sub-foveal choroidal thickness significantly decreased at 9 months follow-up. Studies have demonstrated that VEGFs plays a trophic role on the choroidal vasculature. [14] Therefore, by blocking the action of these growth factors with anti-VEGF therapy, the permeability of the choroidal vasculature decreases, which can be appreciated by a decrease in choroidal thickness.

There are limited data on the efficacy of aflibercept on SFCT in treatment naïve patients as most previously published studies have evaluated the efficacy of aflibercept in patients with

DME unresponsive to previous anti-VEGF therapy. Having said this, some of these studies did not correlate these changes with anatomic and functional outcomes while others have demonstrated significant changes in choroidal vasculature and blood flow and correlation between the central retinal thickness and the choroidal blood flow following intravitreal injection of anti-VEGFs. [9, 15]

With continuing debate regarding choroidal thickness in DME patients, it may be prudent to mention here that there are some studies which have found no significant changes in choroidal thickness after the treatment with anti-VEGF agents. A retrospective study in patients with DME (n=33), did not find any correlation between choroidal thickness and anatomical/functional outcome despite a decrease in central choroidal thickness following anti-VEGF therapy. [16] A Turkish study (n=90) retrospectively evaluated changes in central choroidal thickness, central macular thickness, and best-corrected visual acuity at 2-years in DME patients following aflibercept or ranibizumab injections. The authors did not find any significant decrease in central choroidal thickness after treatment. [17]

A study by Reyess et al observed that baseline sub-foveal choroidal thickness may help predict which patients with DME will respond more favourably to intravitreal anti-VEGF therapy in short term. In this study, eyes with a thicker baseline sub-foveal choroidal thickness had better short-term (3months) anatomic and functional responses. [18] Our study predicted similar changes on long term follow up (>9 months).

Intravitreal anti-VEGF therapy has been shown to cause choroidal thinning in other diseases like age-related macular degeneration as well. A study observed that baseline SFCT was a predictor for treatment in patients with neovascular AMD. They authors observed that a thicker baseline SFCT was a predictor for better visual and anatomic outcomes after 3 and 6 months of ranibizumab therapy. Like our study, the authors had a similar observation as well; patients having a thicker baseline choroidal thickness may represent a subgroup with more preserved choriocapillaris and thus better candidates for improvements following anti-VEGF therapy. [19]

The exact reason for the paradoxical response to intravitreal aflibercept observed in our study is not clear. It is possible that intravitreal aflibercept has a waning effect after initial resolution (after 9 -12 months of therapy). Second, it could be due to poor glycemic control and worsening of DME after 9 months.

A recent study by Valentim et al assessed the relationship between baseline SFCT and BCVA and time to DME resolution following intravitreal injection of aflibercept (n=558). The authors found that as compared to controls, eyes treated with aflibercept had a higher DME resolution rate

(2.5 times) with median resolution time of 7.6 months. A thicker baseline SFCT and better BCVA had a lower resolution rate. The time to DME resolution was not associated with any baseline factor. Although outcomes were not directly correlated with baseline SFCT, a thicker choroid implied higher rate of resolution. [20]

Our results are consistent with optimal vision gains and anatomic improvement previously reported in the large double-masked, randomized Phase III clinical trials VISTA-DME and VIVID-DME trials. In these trials, patients were randomized to receive intravitreal aflibercept injection 2 mg every 4 weeks (n=290), 2 mg every 8 weeks (n=286) after five initial monthly doses, or macular laser photocoagulation (n=286). [21]. Although ETDRS gain in our study with 14 ETDRS letters was better than these studies, it may not be justifiable to draw direct conclusions regarding the efficacy of this treatment schedule with other treatment schemes as ours as only one loading dose phase was analyzed in these trials.

Other trials have found that the gain in visual acuity in DME is gradual and peak visual acuity is only attained after 6–9 months or longer. [22] This suggests that the intensity of initial treatment phase may be critical for long-term anatomic improvement and visual gain. [23-24]

Our study had several limitations as well. The study design was a non-randomized one with absence of a control arm. Furthermore, choroidal thickness was manually calculated using the Heidelberg measuring software leading to observer bias. The ability of observer to center the enhanced depth image acquisition on the choroid may have also added to this bias.

CONCLUSION

In conclusion, there is significant reduction in SFCT at 9 months after the third intravitreal injection of aflibercept. Patients with thicker baseline SFCT had a better functional and anatomical outcome and can be a predictor for response to treatment with intravitreal aflibercept in previously untreated DME patients. Future studies on choroidal microvasculature or choroidal perfusion evaluation may prove valuable in delineating the role of the choroid in DME pathophysiology.

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