

Randomized Trial of Diabetic Macular Edema Treatment with Fewer Ranibizumab Injections and Focal Laser.

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ABSTRACT- Randomized Trial of Diabetic Macular Edema Treatment with fewer Ranibizumab injections and focal laser.

IMPORTANCE: Several diabetic patients with macular edema can' be helped with fewer ranibizumab injections instead of injection and followed for 24-36 months. focal laser to microaneurysms is not a harmful macular procedure.

BACKGROUND: To prove the efficiency of focal laser and fewer ranibizumab injections in improving the visual acuity (ETDRS letters) and reducing the central subfield thickness (CST).

DESIGN: Prospective randomized study.

PARTICIPANTS: Adults with DME (n=150), baseline visual acuity (BCVA) (40 letters) 20/160– (65 letters) 20/50, and CST $\geq 418 \mu\text{m}$.

INTERVENTION(S) (FOR CLINICAL TRIALS): Participants divided into group A-75 for three ranibizumab injections with deferred argon laser and group B-75 for three ranibizumab injections plus argon laser.

MAIN OUTCOME(S) AND MEASURE(S): The outcomes were the changes in visual acuity (ETDRS letters) and CST, baseline, 3 months, and six months after the last injection plus or deferred argon laser. Visual acuity (ETDRS letters), and CST were analyzed with General linear model, logistic regression and independent t-test in both groups.

RESULTS: The mean improvement in letters score at 39weeks was 7.28 letter in group B versus -0.133 ± 1.15 in group A, (P=.000). The median (interquartile range [IQR]) of visual acuity with Snellen's equivalent at 39weeks was .8 (20/125-20/100) among group A participants and 0.6 (20/80-20/63) in group B participants B (P=.000).

At 39weeks, group A participants had mean CST $539.85 \mu\text{m}$, versus group B participants, the mean CST observed, 489.83

μm (P=.001). The 39weeks reduction of CST in group B was $51 \mu\text{m}$ versus $3 \mu\text{m}$ in group A compared with the baseline CST (P=.001).

The correlation between visual acuity (letter score) and CST was 0.199 at 6 months after the last injection and focal laser, one letter of better visual acuity for every $19 \mu\text{m}$ decrease in macular thickness.

CONCLUSIONS: In 39 weeks study, ranibizumab monotherapy for three months and focal laser to DME can gain ≥ 7 letters improvements and $50 \mu\text{m}$ CST reduction. In 39 weeks, focal laser plus fewer ranibizumab injections can give good results.

Trial registration: The trial is registered at Research Ethical Committee, Ain Shams University FWA000017585 FMASU22/2017, Registered at the US National Institutes of Health (ClinicalTrials.gov- ID: NCT04186702) December 4, 2019- Retrospectively registered.

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KEYWORDS

MACULA- INJECTION- LASER- RANIBIZUMAB- EDEMA- THICKNESS

INTRODUCTION

Now, ranibizumab is anti-VEGF drug approved for diabetic macular edema (DME). Ranibizumab can afford good effect without visual defects of laser treatment¹. Subsequently, due to the effect of repeated ranibizumab in pathophysiology of DR and grades changes, the drug was approved for treating non-proliferative DR in eyes with DME². The Diabetic Retinopathy Clinical Research Network (DRCR.net) reported that, the first- year result of repeated ranibizumab injections was successful and can keep DME dry without additional laser treatment in 44% to 63% of patients. Under repeated ranibizumab injections, Vision loss is not the issue for these patients. 75% of these patients had a visual acuity > 20/32, and 56% of these patients did not require laser treatment over 5 years³. In DRCR.net randomized clinical trial, participants with diabetic macular edema (DME) and vision impairment were assigned randomly to intravitreal 0.5 mg ranibizumab combined with prompt or deferred (≥ 24 weeks) focal/grid laser treatment^{4,5}. Results at 3 years of follow-up suggested that focal/ grid laser treatment at the initiation of intravitreal ranibizumab was no better and possibly worse than deferring laser treatment for ≥ 24 weeks with respect to visual acuity outcomes⁶. Long-term data of ranibizumab treatment became available, allowing evaluation of repeated ranibizumab injections effects and recognizing the recovery versus changes of macular edema patterns⁷. These results support the idea that physicians when treated patients with ranibizumab may have many patients with persistent macular edema and thickened macula despite previous months of repeated ranibizumab injections⁸. The aim of the study is to do post hoc analysis of six months follow up of ranibizumab monotherapy for 3 months plus focal argon laser in diabetic macular edema versus ranibizumab monotherapy alone for 3 months to prove the value of focal argon laser to achieve vision stability and reduce the macular thickness.

PATIENTS AND METHODS

This was a prospective randomized study. The study protocol was approved by the Ethics Committee of Ain Shams University (Registration numbers: FWA 000017585 and FMASU R22/2017) and was also registered as and approved at ClinicalTrials.gov (ID: NCT04186702). The study was carried out in accordance with the tenets of the Declaration of Helsinki, and all participants provided written and informed consent to participate.

A total of 150 patients were enrolled in the study between 2014 and 2016. The inclusion criteria involved patients with focal maculopathy, diffuse macular edema, and diffuse macular edema with ischemic changes. No previous argon laser was given to these patients. We accepted the interrupted perifoveal radial vessels and widening the spaces in between on fundus fluorescein angiography (FFA). We excluded ischemic maculopathy that was associated with grades of non-proliferative changes, or capillary drop out zones presented in the periphery of the macula, patients with ischemic heart disease; hypersensitivity to ranibizumab; uncontrolled glaucoma in either eye (intraocular pressure [IOP] >24 mmHg with medication); evidence of vitreomacular traction (in either eye) or active proliferative diabetic retinopathy (study eye); and ocular conditions in the study eye that required chronic concomitant therapy with topical ocular corticosteroids.

RANDOMIZATION AND TREATMENT

This study was conducted in patients with DME who completed 39 weeks. Randomization assigned 75 patients to group A (control group- ranibizumab monotherapy at 0.5 mg dose for three months) and 75 patients to group B (experimental group- ranibizumab monotherapy 0.5 mg dose for three months and focal/direct argon laser). During the study, the investigators remained masked to the participants group and procedures.

TREATMENT PROTOCOL

Visual acuity (ETDRS letters) and central subfield thickness (CST) were measured, improvement was an increase of 5 or more in ETDRS letters (equivalent to one Snellen line) or a decrease in the CST of 10% or more; and worsening was a decrease of 5 or more in ETDRS letters or an increase in the CST of 10% or more. A longitudinal analysis was performed to compare visual acuity and CST thickness change from baseline for 39-weeks adjusting for baseline visual acuity and baseline CSF thickness. Fundus Fluorescein Angiography (FFA) was done after the three months injections in all participants. Focal/direct argon laser photocoagulation therapy was applied at the end of three months for group B patients. Six months after, OCT and visual acuity (ETDRS letters) were done for all participants. The primary outcome measure was the mean change in visual acuity (ETDRS letters) from baseline to six months visit after the last injection (control group) and focal laser (experimental group) with adjustment for baseline visual acuity.

INJECTION TECHNIQUE AND FOCAL ARGON LASER PROCEDURE

We followed the guidelines for anti-VEGF injections. After the eye had been prepared in a standard fashion using 5% povidone-iodine, an eyelid speculum was used to stabilize the eyelids, and the ranibizumab volume 0.05 ml (0.5 mg) was injected 4 mm posterior to the limbus through the pars plana with a 30-gauge needle under topical anesthesia. We used post-injection antibiotics. Laser photocoagulation (focal/direct) was performed after the third injection in group B participants. Direct laser to all leaking microaneurysms in areas of retinal thickening in macular area, 50µm-100µm spot size, 0.05 to 0.1 second duration. We used green wavelengths laser beam (Visulas 532 machine). Endpoint of laser burn was the colour change of microaneurysm or at least a mild grey-white burn evident beneath microaneurysm. The laser reaction was faint bleaching, not aggressive bleaching (creamy or dense white).

STATISTICAL ANALYSIS

Demographic, preoperative data of both groups (control group and experimental group) were compared. The quantitative variables were analyzed between groups using the independent t-test. The qualitative variables were analyzed using a Pearson chi-square test and Fisher's Exact Test. The mean change in visual acuity (ETDRS letters), and CST were analyzed with Mann-Whitney-test and independent t-test. General linear model and logistic regression were used for visual acuity (ETDRS letters), and CST analysis in both groups. The sample size was estimated (pre hoc test) based on the results of Bressler, et al. Repeated injections were required every 4 weeks if there was successive improvement in visual acuity (≥5 letters) or OCT(CST change of ≥10%) and vision remained worse than 20/20 with a CST ≥ 250 µm starting at 24 weeks after initiating ranibizumab treatment. In this study, we considered a study power at 0.8 with α of 0.05.

RESULTS

The ages of the participants varied between 65 - 55 years (the average age was 59.32 years ±2.79). In group A the average was 59.41 ±2.87, in group B the average was 59.24 ± 2.73 (P=.71). Eighty-three participants (55.33%) were females and sixty-seven (44.66%) were males. In group A, forty-two participants were females (56%), thirty-three were males (44%), in group B forty-one were females (54.6%) and thirty-four were males (45.4%) (P=.59). Participants had hypertension and diabetes at least 10 years duration (10-20 years). Ninety per cent of the involved participants had type-2 diabetes (135 type-2 diabetes/15 type-1 diabetes), and the mean duration of diabetes was 12.73±2.14 years. Seventy participants (47%) had hypertension, thirty (43%) in group A, and forty (57%) in group B. Sixty participants (40%) were cigarette smokers, twenty-seven (45%) in group A and thirty-three (55%) in group B. Lipids levels were higher in thirty patients (20%), twelve (40%) in group A and eighteen (60%) in group B. Sixty-four (42.66%) patients are under insulin therapy, thirty-six (56.25%) in group A, and twenty-eight (43.75%) in group B table-1.

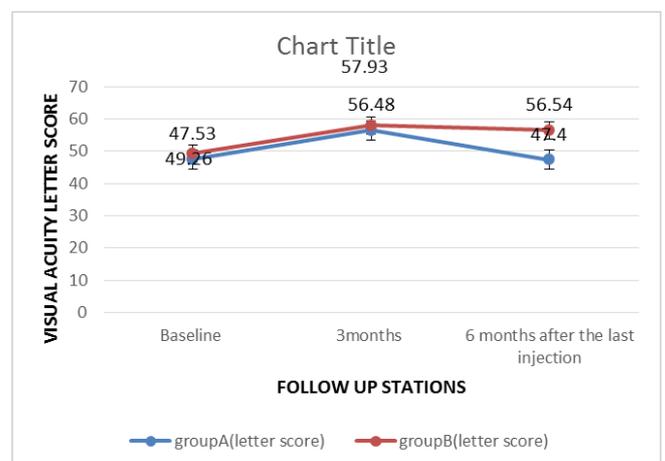
	group)	laser group)	
sex	42/33	41/34	.871*
Age	59.41 ±2.87	59.24 ± 2.73	.706*
Duration of diabetes	10-20years 12.73± 2.12	10-20years 12.73± 2.17	.104**
Insulin taken	36	28	.189*
Hypertension	30	40	.103*
High Lipids level in blood	12	18	.542**
Cigarette smokers	27	33	
visual acuity (ETDRS letters) Median IQR	1.176 .18	1.00 .18	.113**
Baseline macular thickness	542.85± 47.13	541.22± 52.58	.842*

Table 1. Patients data and demography of both groups in the study

*assessed by independent t-test

** assessed by Mann-Whitney-test

The mean follow-up period was 385.17 ± 6.34 days (range, 370 -395 days) for group A and 385.08± 7.23 days (range, 370 -400 days) for group B (P=.93). In both groups the baseline visual acuity (ETDRS letters) varied between (40 letters) 20/160- (65 letters) 20/50, the median and IQR were .80, .18 in group A and .70, .18 in group B (P=.262). The median (interquartile range [IQR]) among group A and B participants, was .6 (20/80-20/63) at three months (P=.369). The median (interquartile range [IQR]) of the best corrected visual acuity with Snellen's equivalent six months after the last injection was .8 (20/125-20/100) among group A participants and 0.6 (20/80-20/63) in group B participants B (P=.000) Fig-1.



Characteristic items	Group A (ranibizumab)	Group B (ranibizumab+)	P value
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Fig-1. Mean change in visual acuity (letter score) during 39 weeks follow-up. Visual acuity improved 7 letters. Baseline and three months Letter scores were similar. Difference in letter score detected at six months after the last injection with prompt versus deferred focal laser). P value adjusted for baseline visual acuity = 0.000.

In group B, 4eyes (5%) gained ≥ 5 ETDRS Letter, and 71eyes(95%) gained ≥ 10 - ETDRS Letter at six month after the last injection and laser,table-2.

Table-2, The visual acuity (ETDRS letters) outcomes of both groups.

*assessed by independent t- test

In group A, six months after the last injection, 74 participants were stable without gaining letters and one participant had lost 10 letters from baseline. The mean improvement in the visual acuity (ETDRS letters) six months after the last injection and laser in group B was 7.28 ± 1.17 versus -0.133 ± 1.15 in group A (Mean Difference= 7.41 , 95% CI: $7.79- 7.04$, $P=.000$). The baseline CST in group A, B were $542.85 \pm 46.81 \mu m$, and $541.23 \pm 52.23 \mu m$ ($P=.842$). In group A participants treated with ranibizumab monotherapy, the mean CST observed at baseline was $542.85 \pm 47.13 \mu m$, and $539.85 \pm 47.12 \mu m$ six months after the last injection ($P=.70$). In group B participants that treated with ranibizumab monotherapy for three months then applying focal laser, the mean CST observed (prior ranibizumab: $541.23 \pm 52.59 \mu m$, six months after the last injection and laser: $489.83 \pm 51.77 \mu m$ ($P=.001$) Fig-2.

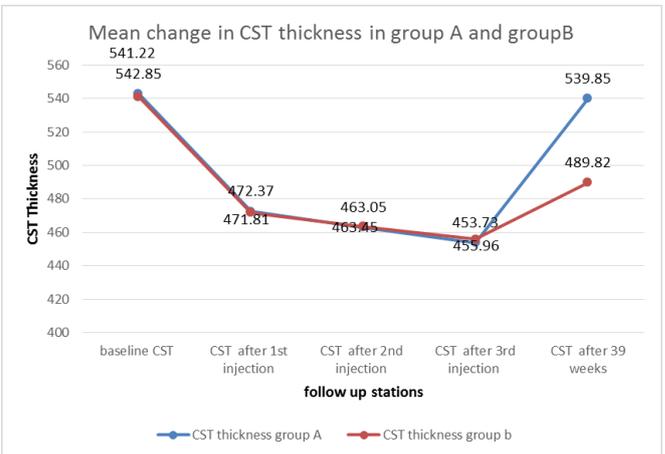
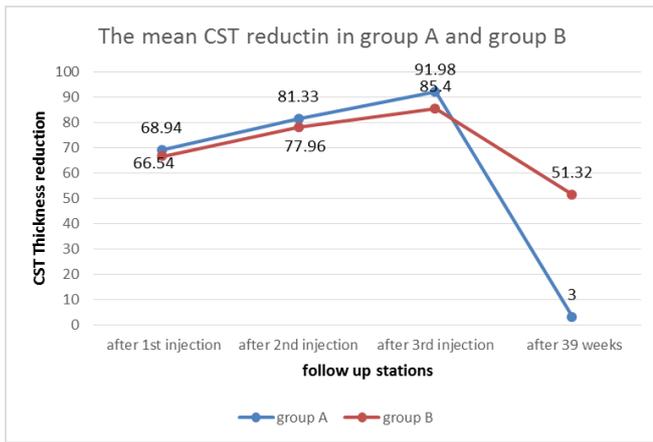


Fig-2 Mean change in central macular thickness (CST) over time. At baseline, 1st, 2nd, 3rd injections the mean CST was nearly similar in both groups. At 39 weeks the mean CST in group B was reduced. P value adjusted for baseline central retinal thickness = 0.001.

A progressive reduction of CST in group A participants (68, 81, 91 μm) was observed during ranibizumab monotherapy for 3 monthly injections. Six months after the last injection, the reduction of CST in group A participants was 3 mm compared with the baseline CST Fig-3.

The visual acuity (ETDRS letters) outcome	Group A (control group)	Group B (experimental group)	P- value
No. of eyes	75	75	
Mean baseline visual acuity (ETDRS letters) visual acuity letter score and Snellen equivalent	47.53± 9.73 20/100-20/125	49.27 ± 9.10 20/100-20/125	.262*
Mean visual acuity (ETDRS letters) at 3 months and Snellen equivalent	56.48 ± 10.56 20/63-20/80	57.93± 9.12 20/63-20/80	.369*
Mean visual acuity (ETDRS letters) at six months after the third injection , focal laser and Snellen equivalent	47.4 ± 9.77 20/100-20/125	56.54± 8.93 20/63-20/80	.000*
categorical baseline visual acuity (ETDRS letters) at six months after the third injection , focal laser and Snellen equivalent (no of eyes) in group A, B	Single case had 10 letter score worsening 74 cases had no letter score improvement	4 eyes had ≥ 5 letter score improvement 71 eyes had ≥ 10 letter score improvement	



injection			
and laser			
follow up			

Table-3. Central Subfield Thickness (CST) Outcomes in A and B groups.

*assessed by independent t- test

In fig-4, 5 the scatterplot diagrams cleared the correlation between the six months letter score result, baseline letter score and 3 months letter score outcomes in both groups.

Fig-3 CST thickness reduction overtime, after 1st,2nd, 3rd ranibizumab injections, the mean CST reduction were nearly similar in both groups. At 39 weeks, there was significant CST reduction in group B. P value adjusted for baseline CST thickness = 0.001.

A progressive reduction of CST in group B participants (66, 77,85 µm) was observed during ranibizumab monotherapy for 3 monthly injections. Six months after the last injection and laser, the reduction of CST in group B participants was 51 µm compared with the baseline CST (mean difference =-48.32, 99% CI: -50.54 to -46.1, P = 0.000) table- 3.

The CST outcome	Group A (ranibizumab group)	Group B (ranibizumab+ laser group)	P value
CST at baseline — µm	542.85 ± 47.13	541.22±52.58	.842*
CST after the third injection	453.73 ± 43.61	455.96± 51.72	.776*
Mean CST reduction after the third injection — µ m	91.98 ± 9.18	85.4±9.13	.001*
CST six months after the third injection and laser follow up	539.85 ± 47.44	489.82 ± 52.11	.001*
Mean CST reduction six months after the third	3 ± 5.00	51.32 ± 8.36	.001*

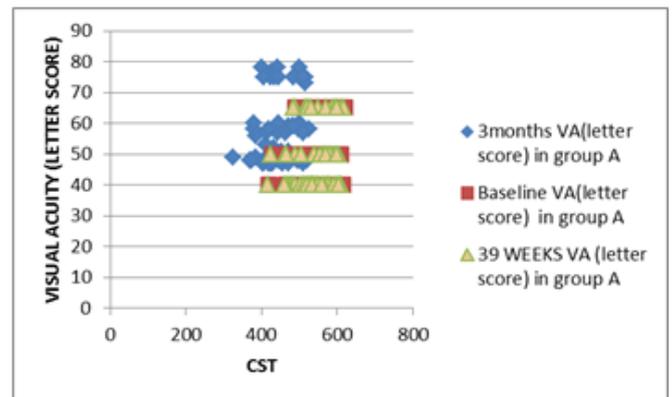


Fig-4 Scatterplot comparing concurrently measured CST(macular thickness) and visual acuity(letter score) at baseline,3 months after, and 39 weeks after in 75 participants-group A. The correlation was found between baseline and 39 weeks measures.

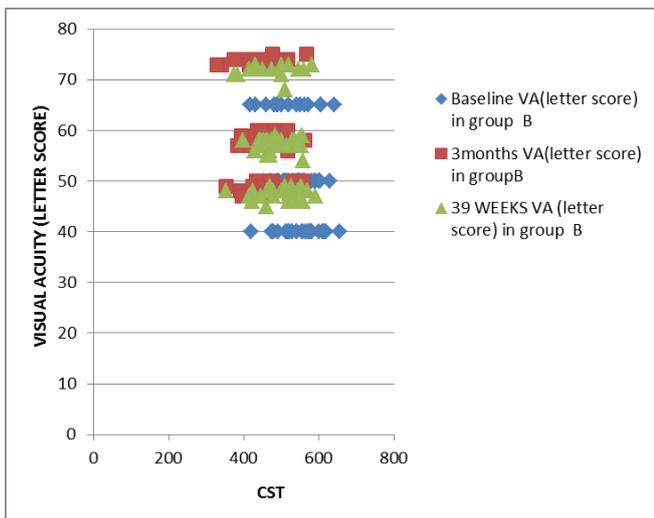


Fig-5 Scatterplot comparing concurrently measured CST(macular thickness) and visual acuity(letter score) at baseline,3 months after, and 39 weeks after in 75 participants-group B. The correlation was found between 3 months and 39 weeks measures.

With logistic regression, the correlation between visual acuity (letter score) and CST was 0.199 at 6 months after the last injection and focal laser, one letter of better visual acuity for every 19 μm decrease in macular thickness. No final resolution of DME and macular thickness in both groups at the last visits. However, GLM multivariate analysis of letter score and CST reported that the power of adding focal laser after three repeated ranibizumab injections and their great effect (P=.001, PES=.98). In both groups, no manifestations of endophthalmitis or traumatic cataract in our study eye over the 12 months follow up.

DISCUSSION

In our study, the visual acuity (ETDRS letters) and central macular thickness improved significantly in diabetic macular edema cases on using the focal/direct laser after three ranibizumab injections. The effect of focal laser after three ranibizumab injections was clinically and statistically significant. In group B, the success rate was 98% at six months follow up after three ranibizumab injections and focal laser. In DRICR.net, at the one-year visits, a 9.2 letter score mean improvement in the visual acuity, and 141 μm mean reduction in CST among eyes at the one-year study (52 weeks)¹⁰. In our study (39 weeks), 7.28 letters mean improvement in the visual acuity letter score, and 51.32 μm mean reduction in CST among eyes in group B at 6 months follow up after three ranibizumab injections plus focal laser. The report of 1-year study results demonstrating an improvement in mean visual acuity in eyes with vision loss from DME involving the foveal center that had been treated with ranibizumab, the question of whether this improvement could be safely sustained over time and, if so, how many treatments were given within the DRICR.net protocol remained¹¹. Three ranibizumab injections plus focal laser in 39 weeks study gave good results with 6 months free of ranibizumab injections. The added focal laser will help the vision without diffuse atrophy to the macular area. The average visual acuity gain at 6 months was maintained with a smaller number of ranibizumab injections. In DRICR net the adding laser will reduce ranibizumab injections (a median

difference of 4 injections between groups), and less visual gain¹². The observed letter score difference in DRICR net that favored the ranibizumab plus deferred laser group may be related to a greater number of ranibizumab injections during follow-up in the deferred laser group. In addition, the observed letter score difference may be related to a potentially destructive effect of the macular laser treatment required. In DRICR net studies all eyes at baseline assigned to ranibizumab combined with prompt focal/grid laser group but given to less than half of the ranibizumab combined with deferred focal/grid laser group¹³. Laser effect can increase over time, and ranibizumab injection has a prompt effect but without important increase over time¹⁴. In our study focal laser was limited, selective and touched the obvious lesions (leaking microaneurysms). We did not give laser for diffuse macular edema and thickened macula (grid pattern). We refused starting the procedure with laser therapy instead of ranibizumab injections. The deferred ranibizumab injection and using laser will lead to damage the neurosensory layers and may end with delaying visual recovery so laser is used after ranibizumab injection to minimize the damage and help visual recovery⁵. In our study three ranibizumab injections (loading injections) was applied at first to reduce the macular thickness and minimize the laser power used before attacking the microaneurysms in macular area. In addition, the direct laser to the microaneurysms will reduce the number of shots instead of grid laser that can produce diffuse macular atrophy. Our protocol of three loading ranibizumab injections followed by focal laser can stabilize the vision and reduced the injection frequency. The treatment goal in the population is to stabilize the visual function without ocular complications like increasing IOP, cataract, progression or diffuse macular atrophy after extensive and diffuse macular laser with high power. Bressler, et.al reported the importance of the combined therapy ranibizumab with argon focal/grid macular laser for patients with DME¹⁴. This is agreed our protocol. DRICR.net allowed focal/argon laser if there was thickened edematous macula without improving with repeated ranibizumab injections and associated with visual loss. Laser can apply directly (focal) to microaneurysms or multiple shots to areas of thickened retina without microaneurysms (grid pattern)¹⁵.

STUDY LIMITATION

In this trial, the follow up period should be extended to 24-36 months for comparison with the diabetic network studies in chronic DME. If there is worsening of vision, the priority is for ranibizumab injections and focal laser will be done if there is possibility. The relation between macular ischemia, chronic DME, and the response of this modality is not discussed. Persistent/ chronic may be overlapped definition, and the response of each type to anti-VEGF therapy and focal laser may be variable.

CONCLUSION

In 39 weeks study, ranibizumab monotherapy for three months and focal laser to DME can gain ≥ 7 letters improvements and 50 μ m CST reduction. In 39 weeks, focal laser plus fewer ranibizumab injections can give good results.

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