

Comparing Bevacizumab PRN and focal/grid laser for naïve diabetic macular edema. One year results of an open-label randomized controlled trial.

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Background: Diabetic retinopathy is an emerging challenge and burden worldwide and in Viet Nam. Among those patients, diabetic macular edema (DME) is disabling for patients in working ages. Bevacizumab is a popular anti-VEGF using in DME with a relative safety profile and good efficacy in clinical use. However, clinical randomized trials using Bevacizumab PRN in DME treatment is somewhat lacking, especially in Viet Nam population. We conducted an open-label clinical randomized trial comparing Bevacizumab PRN to modified ETDRS focal/grid laser in treating naïve DME patients.

Objectives: Intravitreal injection of Bevacizumab is non-inferior to modified ETDRS focal/grid laser in treating naïve DME using BCVA and central retinal thickness (CRT) change from baseline at 12 months.

Methods: This was an open-label randomized controlled trial. We recruited type 2 diabetes patients with vision loss from naïve DME having BCVA from 20/25 to 20/320 (Snellen equivalent) and CRT ≥ 225 micron on spectral domain optical coherence tomography. Each eye was randomized to at least 3 monthly intravitreal Bevacizumab (1,25 mg) injections until BCVA stabilization then PRN or standard modified ETDRS focal/grid laser protocol. BCVA change within 5 letters was considered stable. Bevacizumab group was followed up with BCVA and CRT every month while Laser group was followed up every three months and both were treated PRN accordingly.

Results: There were 112 eyes of 79 patients were randomized (55 to Bevacizumab, 57 to focal/grid laser). Among those eyes, 39.62% bevacizumab-treated eyes vs 8.93% laser-treated eyes gained at least 15 letters at 12 months ($p < 0.001$). Average letters gained were 12.17 ± 6.65 and 2.11 ± 11.84 accordingly. Average change in CRT were -143.89 ± 127.54 and -89.96 ± 127.62 micron respectively ($p < 0.001$). No serious systemic adverse events were recorded. The most common adverse event in bevacizumab-treated patients was subconjunctival hemorrhages 37%.

Conclusions: Bevacizumab PRN was non-inferior to or better than focal/grid laser in treating naïve DME patients in terms of BCVA and CRT change at 12 months.

Keywords: anti-VEGF, Bevacizumab, Diabetic macula edema, Focal/ grid Laser

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Introduction

According to the latest data from the American Diabetes Association, diabetic retinopathy is the leading cause of blindness in adults aged 20 to 74 years. The incidence of diabetes mellitus in the world is also increasing worldwide, which means that diabetic retinopathy will continue to be a major burden of visual loss and blindness in the coming years. Diabetic macular edema is the leading cause of vision loss in diabetic retinopathy patients. Once the edema has involved macular center, the risk of vision loss is even higher. The risk of severe vision loss (loss of at least three lines) after three years was 33% in the ETDRS study.¹⁰

The standard treatment for diabetic macular edema during the past five decades is focal/ grid photocoagulation. However, the therapeutic effect of this method is relatively low, which only reduces the risk of moderate and severe vision loss by 50%.¹⁰ In addition, photocoagulation was significantly less effective with diffuse macular edema with only 14.5% visual improvement.⁷ The DRCR.NET study also found that proportion of visual acuity improvement ≥ 5 letters were 51%, 47%, and 62% at 1, 2 and 3 years, respectively.² The anti-VEGF therapy has recently been shown to have good short-term efficacy by multiple clinical trials.^{1,9} The standard of care of anti-VEGF for diabetic macula edema is Ranibizumab and Aflibercept. Although not officially approved for use in the eye, Bevacizumab, with its cheap and widely available advantage, is one of

the most used anti-VEGF drug in developing world. In CATT study, monthly dosing Bevacizumab has been shown to be non-inferior to Ranibizumab for the treatment of wet AMD. There are some clinical trials using Bevacizumab for the treatment of diabetic macular edema¹¹ and have shown encouraging visual results. In Vietnam, most physicians use the Bevacizumab PRN regimen for diabetic macula edema but robust clinical trials data to support its use are still lacking. To provide evidence-based data on this subject, we compared Bevacizumab PRN regimen with focal/grid laser in an open-label randomized, one center study.

Material(s) and method(s)

Objective

Visual gain (ETDRS letters) and the reduction in CRT (central retinal thickness) compared to baseline at 12 months.

Inclusion criteria

The study subjects will be selected from diabetic macula edema Patients visiting Ho Chi Minh City Eye Hospital from December 1st, 2011 to April 30th, 2014. Patients must be 18 years or older and consent to participate in the study. Eligible criterion for each eye included in the study are the followings:

- Never treated DME before
- BCVA ≥ 19 letters (20/400 Snellen equivalent) and ≤ 80 letters (20/25).
- Clinical significant macula edema
- Central retinal thickness $\geq 225 \mu\text{m}$

Both eyes of the same patient were included in the study only when both eyes met the criteria for inclusion and exclusion at the time of randomisation.

Exclusion criteria

- Previous history of renal failure, kidney transplant or dialysis
- One eye patient
- PRP within 4 months or expected to have PRP in the next 4 months
- YAG laser capsulotomy within 2 months
- Vitrectomy within 6 months

Study design

This was an open-label randomized controlled trial. Baseline characteristics included BCVA, CRT, hypertension, hyperlipidemia, insulin use, smoking history, gender, severity of diabetic retinopathy, lens status. Each eligible eye

was then randomized to at least 3 monthly intravitreal Bevacizumab (1,25 mg) injections until BCVA stabilization then PRN or standard modified ETDRS focal/grid laser protocol. In cases where both eyes were eligible then one eye will be randomized to a treatment arm and the other eye belonged to the remaining arm. BCVA was measured with ETDRS chart and CRT were measured by Cirrus SD OCT at baseline, 3, 6 and 12 months. All procedures including laser photocoagulation, Bevacizumab injections and treatment for complications, if any, were performed by the investigators. Bevacizumab group was followed up with BCVA and CRT every month while Laser group was followed up every three months and both were treated PRN accordingly. Treatment protocols are summarized in Figure 1

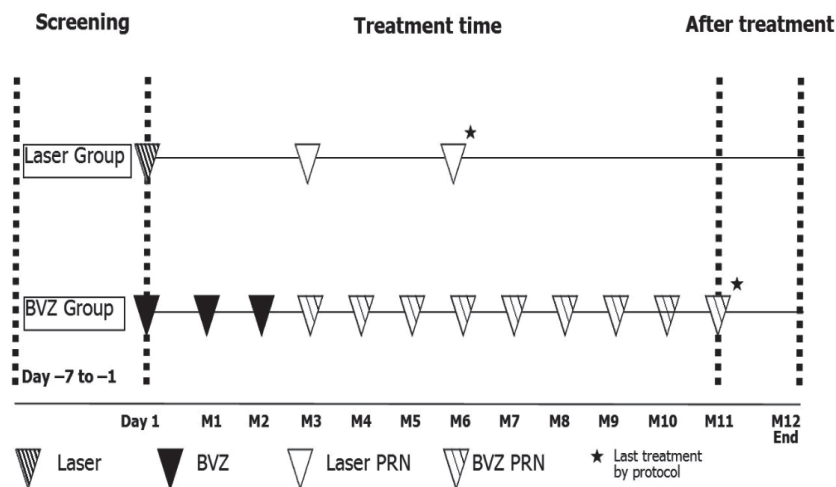


Figure 1 Treatment protocol

Patients in the laser group received focal/grid laser treatment on Day 1 right after randomization. In the case of failure to receive treatment within the day, the treatment must be completed within 2 weeks from randomisation. After the first treatment, the patient was followed up every 3 months and the investigator would classify the status of macular edema as persistent, recurrent or new. Patients received additional treatment if they met one of the following criteria:

- Macula edema worsens.
- Macula edema recurs.
- Appearance of a new macular edema area.
- Macula edema persists within 500 μm from the fovea. Except when the investigator believed there was improvement from previous visit as $> 50\%$ reduction in total macular edema area or $> 50\%$ reduction in total thickening retina area.

In the following cases, there will be no further treatment:

- Macula edema resolved
- Macula edema regressed

The re-treatment time for Laser group should occur only at month 3 or 6. Thus, the number of focal/grid laser treatments for each patient in the Laser group should be at least 1 and a maximum of 3.

In the Bevacizumab group, the patient will be given a monthly injection of Bevacizumab, beginning on Day 1 and continuing until BCVA no longer improving or stable (BCVA change within 5 letters). Stable BCVA was determined through three consecutive monthly follow-up visits during the treatment period (the earliest assessment of visual stabilization was done in the

third month when comparing the 1, 2 and 3 months). If the patient has stable BCVA (at 3 months or any time afterwards), treatment may be discontinued. Patients are monitored monthly for BCVA and disease activity on OCT. If the disease activity was documented, then treatment will be resumed. Disease activity are defined as the followings:

- Visual loss ≥ 5 letters
- Increase CRT $\geq 10\%$ comparing to previous visit
- Recurrent of cystoid macula edema or subretinal fluid
- Recurrent of leakage on FFA

In those cases, patients would be treated monthly with Bevacizumab until VA stabilized again. For VA stability, patient's BCVA needed to be stable in 3 consecutive visits which required at least 2 more treatments. The last treatment was at month 11. The minimum number of injection in this study is 3 and maximum possible injection is 11.

Results

Baseline characteristics

There were 203 patients with diabetic macular edema were eligible for inclusion during screening visits. Of these, 86 patients agreed to participate in the study and signed consent forms. Seven patients were excluded due to exclusion criteria, so the number of patients in the sample was 79. The mean age of the patients was 53.72 ± 9.96 years (32 to 77 years). There were 41 patients (51.89%) were female. The mean diabetes mellitus time was 8.92 ± 4.10 years (2 to 20 years). The mean HbA1C was 8.10 ± 1.74 (4.8 to 13.2). Of the 79 patients mentioned above, 33 (41.77%)

patients had both eyes and 46 (58.23%) patients had one eye being included in the study. Thus, the total number of eyes included in the study was 112 eyes with 79 patients. After randomisation, there were 55 (49.10%) eyes in the

Bevacizumab group and 57 (50.90%) eyes in the laser group. The following table (Table 1) will give more details about the characteristics of the study sample.

Table 1. Baseline characteristics	
Patients characteristics	79 patients
Both eyes included: n (%)	33 (41,77)
Female: n (%)	41 (51,89)
Age: Mean $\pm$ SD (min-max)	53,72 $\pm$ 9,96 (32-77) year
Diabetes time: Mean $\pm$ SD (min-max)	8,92 $\pm$ 4,10 (2-20) year
HbA1C: Mean $\pm$ SD (min-max)	8,10 $\pm$ 1,74 (4,8 - 13,2)
Smoking history: n (%)	33 (41,77)
Insulin user: n (%)	28 (35,44)
Hyperlipidemia: n (%)	49 (62,02)
Hypertension history: n (%)	50 (63,29)
Eye characteristics	112 eyes
OD: n (%)	54 (48,21)
Phakia: n (%)	82 (73,21)
Pseudophakia: n (%)	30 (26,79)
Number of eyes in Bevacizumab group: n (%)	55 (49,10)
Number of eyes in Laser group: n (%)	57 (50,90)
Snellen equivalent: n (%)	
<20/100	12 (10,71)
20/100-20/50	38 (33,93)
20/40-20/25	62 (55,36)
BCVA Mean $\pm$ SD (min-max, median)	64,94 $\pm$ 10,37 (35-80, 66,50) letters
BCVA (Snellen): Mean $\pm$ SD	20/50 $\pm$ 2 hàng
Number of treatments: Mean $\pm$ SD (min-max, median)	
Bevacizumab group	7,29 $\pm$ 2,33 (3-11,7)
Laser group	1,93 $\pm$ 0,75 (1-3,2)
CRT	
226-275 μ m	23 (18,75)
276-400 μ m	49 (43,75)
>400 μ m	40 (37,50)
CRT: Mean $\pm$ SD (min-max, median)	383,04 $\pm$ 123,36 (202 - 861, 363,00) μ m
Leakage in FFA: n (%)	
Focal	42 (37,50)
Diffuse	44 (39,29)
Intermediate	26 (23,21)
Diabetic Retinopathy Severity: n (%)	
No Apparent Retinopathy	2 (1,80)
Mild/ Moderate Non-Proliferative Diabetic Retinopathy	73 (65,18)
Severe Non-Proliferative Diabetic Retinopathy	20 (15,16)
Proliferative Diabetic Retinopathy	17 (17,86)

BCVA and CRT at baseline

Mean BCVA at baseline of Bevacizumab and Laser groups were 63.80 ± 10.71 and 66.04 ± 10.01 letters respectively. Mean CRT at baseline were 398.75 ± 137.50 and 367.89 ± 107.05 μm respectively. The difference between treatment groups in BCVA ($p = 0.31$) and CRT ($p = 0.37$, Mann-Whitney U test) was not statistically significant. In other words, the two groups Bevacizumab and Laser share similarities in BCVA and CRT before treatment.

BCVA after treatment

The mean BCVA of the Bevacizumab group compared with Laser group was as follows:

- 3 months: 8.53 ± 6.49 vs. 0.61 ± 10.3 letters

- 6 months: 9.78 ± 7.86 vs. 2.33 ± 11.89 letters
- 12 months: 12.17 ± 6.65 vs. 2.11 ± 11.84 letters

BCVA in Laser group increased slowly while BCVA in Bevacizumab group increased quickly from month 3. Repeated measures ANOVA showed there was significant difference between the two groups ($p < 0.0001$), between visits ($p = 0.0011$) and no interaction between treatment groups over time ($p = 0.13$). Eyes treated with Bevacizumab had better visual acuity than the Laser treated eyes. By the end of the study at month 12, Bevacizumab group gained +10 letters more than Laser group ($p = 0.0003$; Wilcoxon signed rank test). The following figure (Figure 2) shows BCVA changes comparing to baseline.

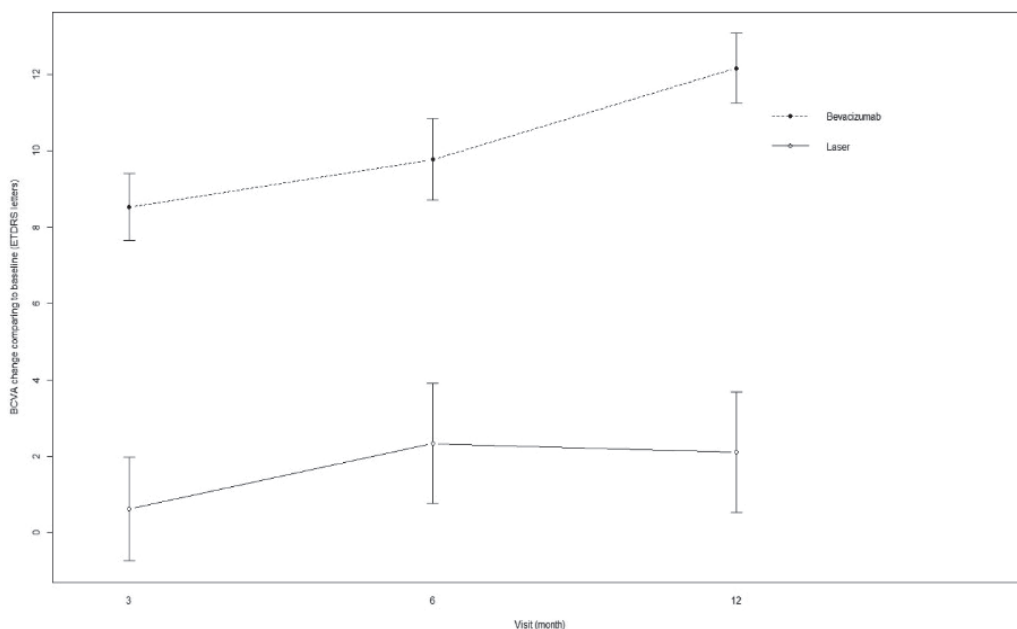


Figure 2. BCVA change comparing to baseline by groups

In this study, thirty-three (41.77%) had both eyes participating in the study, with one eye in the Bevacizumab group and the other in the laser group. Mean BCVA in Bevacizumab and Laser groups in these patients was 65.73 ± 10.41 and 64.85 ± 9.94 letters respectively. Thus, baseline BCVA of the two groups was similar ($p = 0.50$, Wilcoxon signed rank test).

The mean BCVA of the Bevacizumab group compared with the laser group was as follows:

- 3 months: 8.27 ± 7.09 vs. 1.52 ± 9.16 words
- 6 months: 9.58 ± 8.85 vs. 5.45 ± 8.48 words
- 12 months: 11.69 ± 7.46 vs. 4.25 ± 8.64 words

Repeated measures ANOVA showed that there was a significant difference in BCVA between the two groups ($p = 0.0011$), between visits ($p=0.0062$),

There was no interaction between treatment groups over time ($p = 0.67$). In addition, eyes treated with Bevacizumab gained +7.5 more letters comparing to laser treated eyes at month 12 ($p = 0.0003$, Wilcoxon signed rank test).

At month 12, BCVA gained 15 letters or more in Bevacizumab group was 39.62% while that of the laser group was 8.93% ($p = 0.0004$, Chi-squared test). BCVA gain 10 letters or more was 64.15% in Bevacizumab group, and 26.79% in Laser group ($p = 0.0002$, Chi-squared test). BCVA gain 5 letters or more in the Bevacizumab group was 88.68% and that of the Laser group was 48.21% ($p < 0.0001$, Chi-squared test). In the Bevacizumab group, none of the eyes lost 15 or more letters while the laser group had 8.93%, but the difference between the two groups was not statistically significant ($p = 0.057$, Fisher Exact Test). These statistics are detailed in Table 2.

Table 2. Proportion of BVCA change by groups

Proportion % (n/ Total)	Bevacizumab	Laser	P value
BCVA gain ≥ 15 letters	39,62 (21/53)	8,93 (5/56)	0,0004 (Chi-squared)
BCVA gain ≥ 10 letters	64,15 (34/53)	26,79 (15/56)	0,0002 (Chi-squared)
BCVA gain ≥ 5 letters	88,68 (47/53)	48,21 (27/56)	<0,0001 (Chi-squared)
BCVA loss ≥ 15 letters	0 (0/53)	8,93 (5/56)	0,057 (Fisher Exact)

CRT change after treatment

The mean CRT change of the Bevacizumab group compared with the laser group was as follows:

- 3 months: $-112,8 \pm 123,67$ vs $-34,63 \pm 89,98 \mu\text{m}$
- 6 months: $-135,72 \pm 121,93$ vs $-71,37 \pm 127,55 \mu\text{m}$
- 12 months: $-143,89 \pm 127,54$ vs $-89,96 \pm 127,62 \mu\text{m}$

CRT in Laser group slowly regressed while CRT in Bevacizumab group regressed significantly from month 3 (Chart 2). Repeated measures ANOVA showed that there was a significant difference in CRT change between the two groups ($p = 0.03$, between visits ($p < 0.0001$), There was no interaction between treatment groups over time ($p = 0.10$).

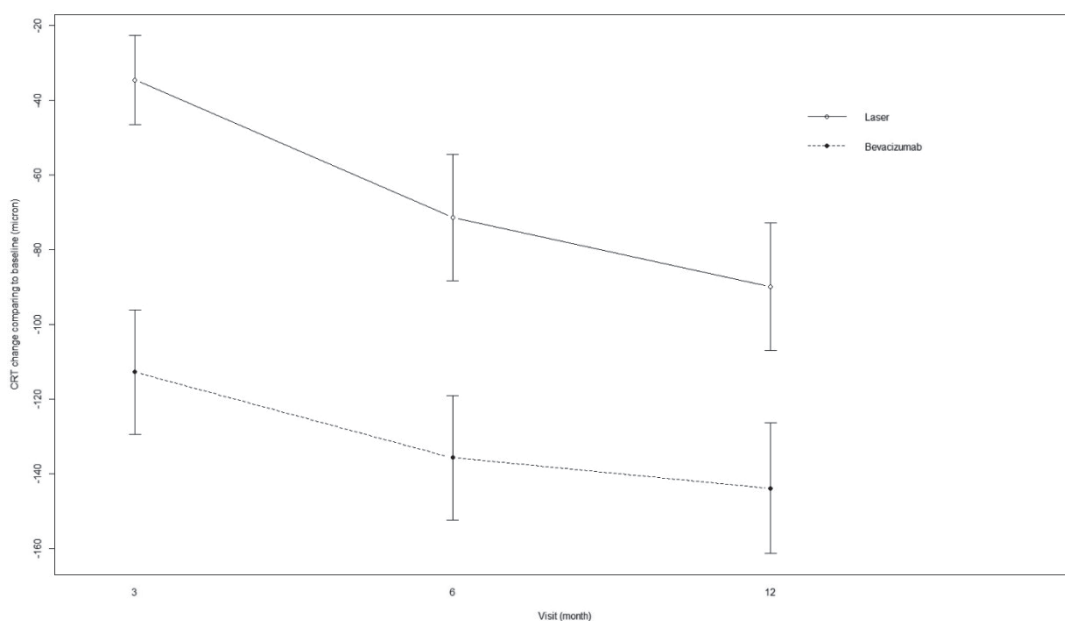


Figure 3. CRT change comparing to baseline by groups

Discussion

In this study, there were 79 patients with 112 eyes participating in the study. The Bevacizumab group had 55 eyes and the Laser group had 57 eyes. Follow-up completion rate at 6 and 12 months were 99.11% and 97.32% respectively. The proportion of men and women in this study is similar. Mean age in the sample was 53.72. There were 72% of patients enrolled in the study with HbA1C > 7. This indicated a poor glycemic control. In addition, about 50% of patients have hyperlipidemia and/or hypertension. Of the 79 patients enrolled in the study, 28 (35%) were treated with insulin. Mean visual acuity of patients in the study was 65.95 ETDRS letters (20/50 Snellen equivalent). Sixty-seven percent of patients had mild/moderate diabetic retinopathy. Median number of

treatments for Bevacizumab group was 7 and Laser group was 2.

BCVA of the two groups Bevacizumab and Laser were similar before treatment. The treatment outcome of the Bevacizumab group was better than that of the laser group at all time points in the study at 3,6 and 12 months. BCVA gain in Bevacizumab group was two lines (10 letters) better than that of the laser group at 12 months. There were 77.36% (approximately 4/5) patients treated with Bevacizumab had BCVA at 12 months $\geq$ 20/40 vs 51.49% in the laser group. This level of BCVA is an important milestone in which the patient could function normally, such as driving a car, watching television and reading. The number of eye gain at least 3 lines (15 letters) in the Bevacizumab group was 39.62% which

was 4.4 times higher than the laser group at 8.93%. No patients in the Bevacizumab group lost three or more lines compared with 8.93% of the laser group. Thus, treatment with bevacizumab has a significantly higher rate of visual acuity gain and visual loss reduction compared with laser treated eyes. These observations are well comparable to many other studies in the literature.^{5,8,12.}

Conclusion

Bevacizumab PRN was more effective in treating diabetic macular edema than a focal/grid laser in this 12-month period study for both visual acuity and reduction in CRT for diabetic macular edema treatment.

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