Indian Journal of Clinical and Experimental Ophthalmology 2021;7(1):234–239

Content available at: https://www.ipinnovative.com/open-access-journals

Indian Journal of Clinical and Experimental Ophthalmology

Journal homepage: www.ijceo.org

Original Research Article

Effect of intravitreal bevacizumab in the uninjected fellow eye of patients treated for retinal disorders

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ARTICLE INFO

Article history:
Received 28-02-2020
Accepted 06-08-2020
Available online 01-04-2021

Keywords:
Bevacizumab
CRVO
PDR

ABSTRACT

Introduction: Elevated levels of VEGF is implicated in the pathogenesis of ocular neovascular diseases such as exudative age-related macular degeneration, proliferative diabetic retinopathy, diabetic macular edema, central and branch retinal vein occlusion, neovascular glaucoma, and retinopathy of prematurity. Bevacizumab a full-length humanized murine monoclonal antibody is being used as an off-label drug in the treatment of above disorders. When administered intravitreally, bevacizumab may have a therapeutic effect in the uninjected fellow eye. The objective of the present study is to determine the effects in the untreated fellow eye of intravitreal bevacizumab after a single dose in the contralateral affected eye in patients with similar retinal pathology.

Materials and Methods: The study was a non-randomized, interventional prospective study. Thirty consecutive patients with similar retinal pathologies in both the eyes were enrolled. All patients in the study underwent a detailed ophthalmic examination including a dilated fundus examination. All patients underwent fundus fluorescein angiography and optical coherence tomography of macula. All suitable patients identified were given intravitreal injections of 1.25 mg bevacizumab. The eye to be injected was selected based on the severity of pathology, affecting the macular status, as depicted by the clinical picture, visual acuity, OCT and FFA. The injections were given under topical anaesthesia. Patients were subsequently followed up on day 2, day 7 and day 21. After 4 weeks FFA and OCT were repeated. The results were tabulated and statistical analysis was done.

Results: The study included 30 eyes of 30 patients with similar retinal pathology in both the eyes the mean age of patients was 64 yrs. 10 eyes had AMD, 9 eyes had PDR, 5 eyes had CNVM, 3 eyes had CME, 2 eyes had myopic CNVM, 1 eye had CRVO. The mean visual acuity at presentation in the uninjected fellow eye was 0.69 ± 0.41 log MAR units. All patients received atleast one intravitreal injection of bevacizumab 1.25mg in one of the affected eyes and the response was observed in the fellow eye. Among the 30 patients who received injection, 29(72.5%) patients showed some improvement in visual acuity chart after the first injection in the fellow eye and in 11(27.5%) patients vision remained same. The initial improvement was seen within one week in most patients. The mean central macular thickness in the fellow eye on OCT at baseline 515.64 + 1.

1. Introduction

Vascular endothelial growth factor (VEGF) is an agent which induces angiogenesis in a variety of in vitro and in vivo models. VEGF A is known to be a main promoter

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https://doi.org/10.18231/j.ijceo.2021.048

of vascular permeability and endothelial cell proliferation and is thus known as a master regulator of angiogenesis.[1–3] VEGF acts a pluripotent growth factor, essential for a variety of processes including maintenance of the adult microvasculature, neuronal survival, and other physiologic processes such as trophic maintenance of ocular tissues.[4] Sufficient concentration of VEGF needs to be maintained in the eye to sustain normal functions. Elevated levels of VEGF is implicated in the pathogenesis of ocular neovascular diseases such as exudative age-related macular degeneration (AMD),[5] Proliferative diabetic retinopathy (PDR), Diabetic macular edema (DME),[6] central and branch retinal vein occlusion,[7] Neovascular glaucoma,[8] and retinopathy of prematurity.[9] VEGF increases retinal vascular permeability by increasing the phosphorylation of tight junction proteins.[3] The advent of intravitreal therapies targeting VEGF's has brought a paradigm shift in the treatment of ocular neovascular diseases. Anti-VEGF's presently in use are, pegaptanib sodium, and ranibizumab, both having received FDA approval. Bevacizumab a full-length humanized murine monoclonal antibody (IgG1) related to ranibizumab is being used as an off-label drug. Recent studies have demonstrated the usefulness of an intravitreal injection of bevacizumab in the reduction of macular edema secondary to central retinal vein occlusion, vascular permeability and fibrovascular proliferation in retinal neovascularization secondary to PDR, and choroidal neovascularization secondary to age-related macular degeneration (AMD).[10]

Bevacizumab is known to increase the risk of thromboembolic events when infused intravenously. However, even when administered intravitreally at much lower concentrations, bevacizumab may have a therapeutic effect in the uninjected fellow eye. The possible mechanism for this is that intravitreal bevacizumab may be able to escape from the eye into the systemic circulation, where it may inhibit VEGF in the other eye. It has been a topic of research and debate about the systemic absorption of anti-VEGF, particularly bevacizumab. Rosenfeld et al. showed the effectiveness of systemic administration of 5 mg/kg bevacizumab for the treatment of AMD, thus demonstrating that the molecule passes from the systemic circulation to the eyes.[11] Recently, Bakri et al. in their study established that a small portion of intravitreal bevacizumab enters the systemic circulation in an animal model.[12] Avery et al demonstrated clinical effects of intravitreal bevacizumab in untreated fellow eyes and found subtle decreased leakage and regression of optic disc proliferations in untreated fellow eyes with proliferative diabetic retinopathy.

The objective of the present study is to determine the effects on CMT and visual outcome, in the untreated fellow eye of intravitreal bevacizumab after a single dose in the contralateral affected eye in patients with similar retinal pathology.

2. Materials and Methods

The study was a non-randomized, interventional prospective study carried out among patients attending Eye OPD of a tertiary care eye centre from July 2015 to 01 Jul 2017. Informed consent was obtained from all the patients. Ethical clearance was obtained for the study. Thirty consecutive patients attending the Ophthalmology outpatient department for various retinal pathologies, which were similar in both the eyes, were enrolled in the study. A complete medical history of diabetes mellitus, renal disease, hypertension, coronary artery disease, cerebro-vascular disease and use of any systemic or ocular medications was noted. Any patient requiring intravitreal anti-VEGF for retinal pathologies which were similar in both the eyes as diagnosed by clinical features, and fundus findings as in AMD, CNVM, CSME, CME, CSR and venous occlusions were included. Patients unwilling to give consent, patients with coexisting diabetic nephropathy, patients with history of thrombo embolic episodes, patients with acute ocular inflammations, patient who had received prior intravitreal injections and on anti-VEGF injections for any other systemic diseasewere excluded. All patients in the study underwent a detailed ophthalmic examination including a dilated fundus examination. Intraocular Pressure (IOP) was measured by applanation tonometry in all the eyes. All patients underwent fundus fluorescein angiography (FFA) Carl Zeiss fundus camera FF450 and Optical coherence tomography (OCT) (Carl Zeiss Meditec, Dublin, CA, USA) of macula. All the investigations were performed by the same surgeon. Systemic examination of the patients was also done and blood pressure recording, urine analysis, blood sugar, lipid profile, plasma glycosylated hemoglobin and ECG were recorded. All suitable patients identified were given intravitreal injections of 1.25 mg bevacizumab. The eye to be injected was selected based on the severity of pathology, affecting the macular status, as depicted by the clinical picture, visual acuity, OCT and FFA.

The injections were given under topical anaesthesia using proparacaine drops. The eye was prepared with three applications of 10% povidone iodine. The eye was held with a Lim's forceps and the intravitreal injection was given through pars plana route at three to four mm from limbus depending on phakic status patients with a 30-gauge needle. The eye was bandaged with an antibiotic eye ointment and the bandage was opened the next day. A single stat dose of Acetazolamide 250 mg was given on the day of the injection. Topical antibiotic and steroid drops were administered six hourly for one week after injection. Patients were instructed to return immediately in case of ocular pain, redness or deterioration of vision.

In the post operative period complications like haemorrhage, infection, uveitis, and any systemic adverse effects were recorded. Patients were subsequently followed up on day 2, day 7 and day 28 with assessment of

best corrected visual acuity, examination of the anterior segment, IOP recording, dilated fundus examination. Cases developed subconjunctival hemorrhage in the injected eye which resolved in 1st week. One case of intraocular inflammation was noticed which subsided with topical steroids. After 4 weeks FFA and OCT were repeated. The results were tabulated and statistical analysis was done using SPSS software with p vale less than 0.05to be significant.

3. Results

The study included 30 eyes of 30 patients with similar retinal pathology in both the eyes who received intravitreal bevacizumab in either of the eyes. The mean age of patients was 64 yrs with a range of 48-78 yrs (Table 1). Out of 30 patients in the study, 21 patients were males (70.0%) and 9 were females (30.0%) (Table 2). 10 eyes had AMD, 9 eyes had PDR, 5 eyes had CNVM, 3 eyes had CME, 2 eyes had myopic CNVM, 1 eye had CRVO (Table 3). Out of 30 eyes in the study, injections were given in right eye in 21 patients and in left eye in 9 patients. 13 patients (43.3%) were pseudophakic and 17 patients (56.7%) were phakic. The mean visual acuity at presentation in the uninjected fellow eye was 0.69 ± 0.41 log MAR units. All patients received atleast one intravitreal injection of bevacizumab 1.25mg in one of the affected eyes and the response was observed in the fellow eye.

Among the 30 patients who received injection, 19(63.3%) patients showed some improvement in visual acuity chart after the first injection in the fellow eye and in 11(36.7%) patients vision remained same (Table 8) [Figure 3]. The initial improvement was seen within one week in most patients. The mean central macular thickness in the fellow eye on OCT atbaseline 515.64 + 191.9 μ. The central macular thickness on OCT after the intravitreal injection in the fellow eye had a mean of 412.2 + 155.6 μ [Tables 4 and 5]. The mean difference in CMT pre and post injection in the fellow uninjected eye was 103.5 μ with a standard deviation of 123.2 μ (Tables 6 and 7) [Figures 1 and 2]. 6 cases developed subconjunctival hemorrhage, in the injected eye which resolved in 1^{st} week. One case of intra ocular inflammation was noticed which subsided with topical steroids.

None of the patients developed cataract, retinal tear, retinal detachment, glaucoma, endophthalmitis in either of the eyes. There were no systemic side effects such as stroke, myocardial infarction, hypertension, proteinuria, and congestive heart failure.

4. Discussion

The present day clinical knowledge approves anti-VEGF injections to reduce macular edema in ocular neovascular diseases such as neovascular age-related

Table 1: Age distribution of the patients

Age (yrs)	No of patients	Sex	
		Male	Female
40-49	1	0	1
50-59	6	3	3
60-69	15	11	4
70-79	8	7	1

Table 2: Gender distribution of patients

Sex	Males	Females
No of patients	21	09

Table 3: The retinal pathology of patients

S. No	Diagnosis	Number (%)
1	AMD	15 (50%)
2	NPDR/PDR with CSME	9 (30%)
3	Post surgical CME	3 (10%)
4	Myopic CNVM	2 (7%)
5	CRVO with CME	1 (3%)

Table 4: Pre- injection central macular thickness in injected eye

Range of Central Macular Thickness	No. of patients
Less than 400 μ	09
401 μ -500 μ	02
501 μ -600 μ	09
601 μ - 700 μ	05
701 μ - 800 μ	03
More than 800 μ	02

Table 5: Post- injection(28 days) central macular thickness in injected eye

Range of CMT*	No. of patients
201 μ-300 μ	08
301 μ -400 μ	06
401 μ -500 μ	08
501 μ -600 μ	04
601 μ - 700 μ	01
701 μ - 800 μ	03
801 μ - 900 μ	0

Table 6: Central macular thickness in the fellow uninjected eye

Range of CMT	No. of patients
201 μ-300 μ	15
301 μ -400 μ	03
401 μ -500 μ	05
501 μ -600 μ	06
601 μ - 700 μ	00
701 μ - 800 μ	01

Table 8: Distribution of visual acuity in the fellow uninjected eye during observation period from Day 0 till Day 28

Visual acuity	No of patients D0	No of patients D1	No of patients D2	No of patients D7	No of patients D28
1/60	1	0	0	0	0
2/60- 4/60	2	4	4	4	4
5/60- 6/60	7	3	1	1	0
6/36- 6/24	7	10	11	11	14
6/18	4	1	2	1	0
≥ 6/12	9	12	12	13	12

Table 7: Post injection central macular thickness in the fellow uninjected eye

Range of CMT*	No. of patients
201 μ-300 μ	15
301 μ -400 μ	05
401 μ -500 μ	07
501 μ -600 μ	01
601 μ - 700 μ	01
701 μ - 800 μ	01

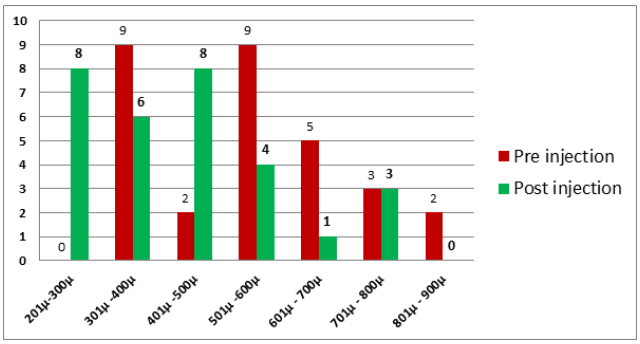

Fig. 1: Showing pre and post injection baseline central macular thickness on OCT in the injected eye

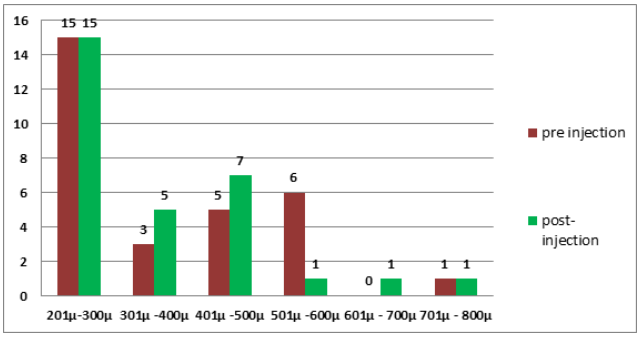

Fig. 2: Showing pre and post injection Baseline central macular thickness on OCT in the Fellow un-injected eye

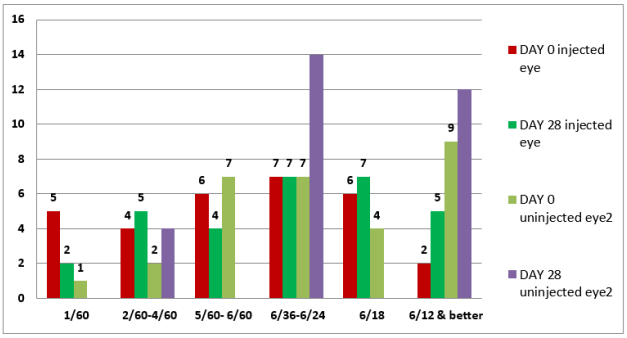

Fig. 3: Best corrected visual acuity of injected versus fellow un-injected eye pre injection (Day 0) and post injection (Day 28)

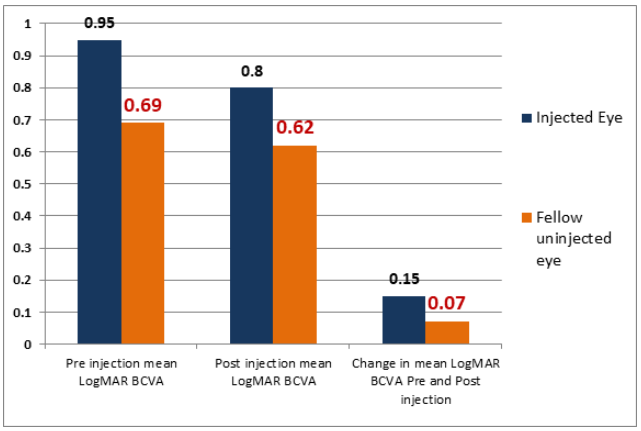

Fig. 4: Comparison of change in mean LogMAR value of BCVA pre and post injection between injected eye and fellow un-injected eye

macular degeneration (NV-AMD),[4] proliferative diabetic retinopathy (PDR) as well as diabetic macular edema (DME)[5] and retinal vein occlusions (RVO).[6] The effect of the intravitreal injections on the fellow uninjected eye has been noted in various case reports. Few studies were conducted to establish this fact but with inconclusive results. The effect in the fellow eye is usually attributed to the systemic absorption of the drug through the vitreous exerting therapeutic effect in the other eye.[8,13] The therapeutic effect in the other eye can be assessed quantitatively by measuring the central

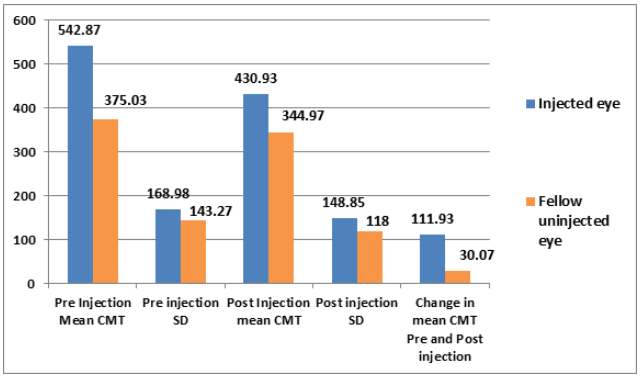

Fig. 5: Showing comparison of CMT changes in injected eye vs fellow un-injected eye

macular thickness.[14–16] This biological effect can further be correlated with the change in visual acuity following the treatment.[17,18] The study included 30 patients who were given intravitreal anti VEGF agents. The mean age was 64.43 yrs with a range of 48-78yrs. The age pattern observed in the study commensurate with the retinal diseases included in the study. AMD and PDR formed approximately $\frac{3}{4}$ of the cases. In Indian eyes AMD has a mean age of 60 yrs[19] and PDR maximally affects 45-64yr age group.[20,21] The sex distribution of patients showed skewing towards male gender with 70% males and 30% females. This gender difference occurred as this study was done in a tertiary care centre where the males in outpatient department outweighs that of females.

The inclusion criteria in the study warranted similar retinal pathology in both the eyes. The diseases included in this study were: AMD (50%), diabetic retinopathy with CSME (30%), CME (10%), Myopic CNVM (7%) and CRVO (3%). This pattern reflects the prevalence of retinal diseases affecting both eyes in Indian scenario and is in accordance with published India literature.[22] In our study Anti VEGF used was bevacizumab in an intravitreal dose of 1.25 mg. Patients were followed up to a minimum of 28 days which corresponds to the half-life of bevacizumab. The study did not ascertain the treatment regimen of various diseases, but rather followed the changes after a single event i.e., Injection bevacizumab, for effects in fellow eye.

The effects of intravitreal bevacizumab were assessed by change in two parameters, CMT and BCVA. Firstly by comparing the pre injection CMT values with post injection values in fellow eye, and further comparing this change with corresponding injected eye. The mean CMT in fellow uninjected eye decreased from a pre-injection value of 375.03μ (Range 212μ - 810μ, SD 143.27μ) to 344.97 μ (Range 178μ - 658μ, SD 118μ) which was statistically significant ($p<0.05$). However, the absolute reduction in mean CMT pre and post injection is 30.07μ which is clinically not significant when compared to absolute reduction in mean CMT pre and post injection of 111.93 μ in injected eyes.

Secondly by comparing the pre-injection LogMAR BCVA values with post injection values in fellow eye, and further comparing this change with corresponding injected eye. The mean LogMAR BCVA in fellow uninjected eye decreased from 0.69 pre-injection to 0.62 post injection. The change of 0.07 LogMAR value was both statistically and clinically insignificant ($p>0.05$). In comparison, the injected eye showed a pre injection LogMAR value of 0.95 decreasing to 0.80 which is both clinically and statistically significant, as has been proved in a multitude of published studies.[8,23] This worked as a control to demonstrate the efficacy of injected drug acting upon the disease in injected eye compared to no effect in the fellow eye. Maximum improvement of visual acuity and decrease in central retinal thickness was seen by second week, which was maintained approximately till four weeks in most of the patients.

No systemic effect due to the intravitreal anti-VEGF, in the form of any thromboembolic or cardio vascular complications, occurred. This was similar to the previous studies, as reported in literature.[24] In addition no serious adverse ocular effects were seen in either eye during the 28 days follow up, minor side effects like redness, watering and foreign body sensation in injected eye resolved within 28 day observation period.

This study proved that when Anti VEGFs are injected in one eye, the effects in fellow eye in terms of change in CMT and BCVA remain clinically non-significant. The statistically significant change in CMT in fellow eye however leaves scope for speculation, as to whether the effect was due to Anti VEGF leaking from the injected eye in blood stream and finding their way to the fellow eye, or this was due to resolution of macular edema in natural course of disease. The visual acuity and macular edema when analyzed in individual cases showed significant clinical improvement in few cases. This observation warrants a larger prospective clinical trial to establish this finding.

5. Source of Funding

None.

6. Conflict of Interest

The authors declare that there is no conflict of interest.

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Cite this article: Mogra S, Reddy S, Satyasri B, Kumar K V P, Kumar P. Effect of intravitreal bevacizumab in the uninjected fellow eye of patients treated for retinal disorders. *Indian J Clin Exp Ophthalmol* 2021;7(1):234-239.