

Original Research Article

Visual outcome versus vision satisfaction after intravitreal Bevasizumb injection in diabetic retinopathy.

Abstract:

Introduction: Diabetic retinopathy as an important complication of diabetes mellitus is a common cause of blindness in diabetic people. There is not available a curable treatment. This study is design to investigate the efficacy of the intravitreal injection of Avastin on visual and patients satisfaction with diabetic retinopathy.

Material and Methods: This study included 30 eyes of 30 patients (mean age: 60.47 ± 8.94 years) with diabetic retinopathy showing no recovery with common treatments. After the intravitreal injection of 1.25mg/0.05ml of Avastin at the day of injection, the examination was performed. In this examination, the resolution of neovascularization, clearance of vitrous and visual acuity versus vision satisfaction were evaluated.

Results: 60% of patients were women (n=18) and 40% were men (n=12). All patients had type 2 diabetes for a period of 8.47 ± 5.28 years (range 2-25 years). Change in best corrected visual acuity (BCVA) in right eye was 0.22 ± 0.63 log MAR which it was statistically significant ($p=0.010$). The BCVA in left eye was 0.31 ± 0.74 log mar that it showed also significant relation ($p=0.020$). BCVA Changes had not a meaningful relationship with age and sex of patients, but had a negative meaningful relationship with duration of diabetes retinopathy in both right and left eyes. ($p=0/048$, $p=0/006$ respectively).

Conclusion: Avastin showed short time statistically significant visual benefit and also improvement in ophthalmic pathology in clinical examination **versus visual satisfaction, however it was not compatible to ask all of the patient's visual satisfaction**. So, the future studies will be needed to determine the therapeutic effect of this treatment option.

Key words: diabetic retinopathy, vision satisfaction, Avastin.

Introduction:

The early treatment diabetic retinopathy study (ETDRS) demonstrated that immediate focal photocoagulation reduced moderate visual loss by 50, this suggests that a distinct subgroup of eyes exists with diabetic macular edema (DME) resistant to conventional laser photocoagulation. [1]

Vitrectomy or application of focal macular laser and panretinal photocoagulation at appropriate disease stages reduces the risk of further vision loss. While triamcinolone 3-year visual benefit was found to be inferior to standard focal macular laser, ongoing research will determine the utility of inhibitors of vascular endothelial growth factor as an additional tool in the management of diabetic retinopathy. [1, 2]

The M. Michaelides et-al finding support the use of bevacizumab in patients with persistent nonischemic center-involving (clinically significant macular edema)CSME but they was not able to find the benefit despite the relatively long duration of CSME and high number of previous laser treatments at baseline. [3]

There are others studies that indicate intravitreal bevacizumab for DME which have severe capillary loss showed beneficial effects on vision and favorable remodeling of the macular architecture. They conclude no major adverse event related to treatment during the 54-week follow-up. [4]

As described by Avery and colleagues it remains unclear how frequently repeat anti-VEGF therapy would be necessary to ensure regression of neovascularization, and panretinal photocoagulation clearly seems to be a preferred treatment for chronic intravitreal injections. [5]

The overwhelming evidence for intravitreal bevacizumab's role in the treatment of retinal disease was our encouragement to do this study which explained our experience with this emerging of treatment.

Material and Methods

The 30 eyes of 30 patients who had CSME or proliferative diabetic retinopathy enrolled in this study. The worse eye or the only one eye underwent intravitreal injection of bevacizumab. Exclusion criteria were intravitreal steroids within the last 4 months, of intraocular injection of anti-VEGF within the last 3 months, macular ischemia more than one disc diameter, and prior history of intraocular surgery within at last 6 months ago. Patients with thromboembolic events or uncontrolled hypertension also excluded of study. Informed consent was obtained from all patients.

A complete ophthalmic examination at baseline and thereafter by every visit during the follow-up, including BCVA using standard Snellen charts, ophthalmoscopy and fluorescein angiography (Topcon, Topcon Corporation, Tokyo, Japan) or Optical coherence tomography (OCT) if needed was done. All the patients completed a follow-up time of at least 3-36 months and filled a satisfaction sheet that the structured patient satisfaction

questionnaire with 1- improved vision 2- No improved vision 3-not noticeable or worsted. Questions with similar inferences had reliable answers and the questionnaire was then administered to descriptive interpretation due to no comparative study groups.

The patients' retinopathy was divided into two groups according to the stage of retinopathy that either have proliferative diabetic retinopathy with vitreous hemorrhage which were the most participant or severe diabetic maculopathy.

The each eye after intervention the related right or left eye follows 17-26 months accordingly. As the small study sample, the most patients have proliferative diabetic retinopathy (24 patients) that recruited in study groups. This limitation was the reason to could not divid the retinopathy in based of stage of retinopathy and could be possible to done statistical test.

The procedure was done under topical anesthesia and after insertion of lid speculum povidone-iodine 5% was applied to conjunctiva and lid margins. The 1.25 mg bevacizumab injections were undertaken with a 27-gauge needle through the supra- temporal quadrant. The patients taken one to three injections and were followed monthly.

To determine the effect of an intravitreal injection of bevacizumab on actively growing new vessels, we chose the variation in vitreous leakage from retinal neovascularization as our primary outcome. The detection of neovascularization of disc and neovascularization of else on FA allowed the use of a systematic anatomical approach to monitor the area of leaking new vessels over time. To determine the effect of an intravitreal injection of bevacizumab on macular edema, we detect the variation on retinal thickness clinically indeed of OCT measurement.

Patients received re injections when there was a recurrence of DME. Recurrence was defined as a decrease of BCVA associated with an increase of intraretinal fluid due to macular edema on OCT and/or FA, after complete or partial resolution in previous follow-up visits.

All visual acuities were converted to logMAR before analysis for statistical purposes. Due to the small number of patients, the Wilcoxon matched pairs test was used for the statistical analysis of the data. A p -value less than 0.05 were considered to be the threshold for significance.

The outcome measurement was comparison of the mean ETDRS BCVA at 3-36 months follow up between pre and post IVB injection. The others variable was relating to safety in ocular side effects and systemic side effects according to patients complain. The third was assessment of visual satisfaction of their visual outcome.

Results

Of 30 patients who enrolled in the study, 40% (No=12) was men and 60 % (No= 18) were female the mean ages was 60.47 ± 8.94 years ranged from 39 to 83 years. (Table 1)

Visual acuity showed improvement objectively, but 53.4% of patients when asking subjectively according the three at all questionnaire was not agree in their visual improvement accordingly as they think but 26.6% patients have noticeable improvement of vision while 20% of patients have not noticeable improvement or also worsted their vision according to before and after bevacizumb interavitreal injection in their eyes. As it showed in figure 1 and table 2, 3 this improvement difference have not a brisk insult subjectively in near of half of patient as we asking about the effect of intravitreal avastin injection on visual effect. The Vitreous hemorrhage and new vessels regressed vigorously after interavitreal injection but after one month again gradually appeared as it showed the same patient in different time of appearing and disappearing rubeosis iridis (figure 2, 3). Complication in this study was retinal detachment after second injection in one patient, two cases also developed the temporary mild anterior uveitis without pain or others eye complain such as vitritis, hypopyon, and blurred vision. The inflammation resolves in few days by topical steroid treatment.

Discussion:

There was clinically significant difference in visual improvement at right and left eye before and after injection, but subjectively by asking the visual improvement satisfaction ratio in near half of our patient's does not have visual outcome satisfaction in spite of this significant difference in objective test evaluation. That it could be due to the attendant of late stage of diabetic retinopathy who had severe maculopathy or proliferative diabetic retinopathy with vitreous hemorrhage (High Risk characteristic) in our patient or as the cost effect of intervention due to socio-economic condition. The studies by Elman and Fernando Arevalo with colleagues about ranibizumab or focal/grid laser, or both they indicate that additional studies are needed to can judge the success criteria which met early in the course of treatment. [6, 7]

So, the other researcher as described in the below are not sure about this therapeutic option, [8, 9, 10] they suggests that intravitreal bevacizumab is not an effective treatment for diffuse DME. An explanation for this different finding was thought to be the criteria they used to define diffuse DME.¹¹, however in contrast there are many reports that emphasis on important therapeutic role and their safety of avastin in diabetic retinopathy b the retinal photocoagulation have a main stay treatment in diabetic retinopathy. [12, 13, 14, 15]

Simo and Hernandez also believed that Bevacizumab is an off-label medicine that many ophthalmologists used it because it is as effective as pegaptanib or ranibizumab but is much cheaper. In this regard, they conclude more clinical trials designed to evaluate not only efficacy, but also systemic adverse effects of anti-VEGF therapy [9] .

Our study showed statistically significant difference in VA outcome after intravitreal bevasizumb injection either due to diabetes maculopathy or proliferative retinopathy, the most excellent response was in the first month post injection. After 3 months of ranibizumb we could not find stable diabetic maculopathy or proliferative diabetic retinopathy either by permanently preventing of retinal and iris neovascularisation or macular edema which gradually appeared again in certain cases. However our finding were not classificate the HbA1c but it was not agree with Matsuda S et al in one direction of their study that it does not show any significant difference related to number of intravitreal injection in the $HbA1c \leq 7.0\%$ group compared to $HbA1c > 7.0\%$ group. They also suggested that glucose regulation can impact the response to anti-VEGF therapy in the management of DME [16] .

Few patient developed mild anterior chamber reaction with full recovery by topical steroid. Except of one case which have two injections due to macular edema and denied operation which lost the left eye after rhegmatogenous and tractional retinal detachment. The questionnaire satisfaction that was prepared subjectively to find how much patient agreement is in their visual improvement approximately half of patient's satisfaction questionnaire was not compatible to visual finding outcome objectively with the second question, so it could be related to the patient's expectation of cost effect based of procedure or may be due to psychological condition in such debilitating diseases and socio economic situation. Therefore in needed to done explanation of treatment outcome to the patients. The Ferenchak and colugos study described twelve eyes of nine patients of intravitreal bevacizumab (IVB) for eyes with recurrent vitreous hemorrhage after vitrectomy for proliferative diabetic retinopathy. They conclude that in their study none of twelve eye required repeat vitrectomy for recurrent VH. Mean follow-up was 22 months (range, 8-42). A mean of 8.1 IVB (range, 1-18) were given Intravitreal bevacizumab was a safe and effective adjunct in this series for the management of recurrent VH after vitrectomy for proliferative diabetic retinopathy [17] . In a review study by Nicholson and Schachat they described in spite of short-term benefit

in visual acuity, but this treatment may be associated with tractional retinal detachment. Finally they concluded despite promising early reports on the safety of these medications, we will be await to knows more results of the safety and efficacy of anti-VEGF drugs for diabetic retinopathy [10] . Our study also showed the same suggestion as above described by them but one case develop retinal detachment.

The Spearman correlation coefficient between age and visual changes before and after injection in the right and left eye dose not demonstrate any significant relationship. ($p = 0.222$, $p = 0.913$). But the Spearman correlation coefficient showed that duration of diabetes has a negative relationship in both eye visions before and after injection. ($p = 0.048$, $p = 0.006$) This means that the longer duration of diabetes reduced the vision improvement change before and after of injection in both eye.

Limitations of our study are nonrandomized, uncontrolled, and retrospective, which preclude any estimation of efficacy or safety of intravitreal bevacizumab. In addition, due to no control group we cannot rule out the possibility of improvement in macular edema might be associated with systemic health attention. The retinal thickness were ≥ 300 micrometres and. patients had controlled diabetes with a mean HbA1c of about 7.7% only in this study without information of it in past. However, the results were very promising but it suggest the need for further investigation.

In summary, although it taken many years of intravitreal bevacizumab injection and the preliminarily reports which claimed stability and improvement in VA, the future over all argumentative reports will be make any specific treatment recommendations. So, in spit of many promising results but it is too soon to judgment the safety and efficacy and cost effectiveness of this treatment.

Reference:

1. Arevalo JF, Fromow-Guerra J, Quiroz-Mercado H, Sanchez JG, Wu L, Maia M, et al. Primary intravitreal bevacizumab (Avastin) for diabetic macular edema: results from the Pan-American Collaborative Retina Study Group at 6-month follow-up. *Ophthalmology*. 2007; 114(4):743-50.
2. Fante RJ, Durairaj VD, Oliver SC. Diabetic Retinopathy: An Update on Treatment. *Am J Med*. 2010 Mar; 123(3):213-6.
3. Michaelides M, Kaines A, Hamilton RD, Fraser-Bell S, Rajendram R, Quhill F, et al. A prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT study) 12-month data: report 2. *Ophthalmology*. 2010; 117(6):1078-1086.e2.
4. Bonini-Filho M, Costa RA, Calucci D, Jorge R, Melo LA Jr, Scott IU. Intravitreal bevacizumab for diabetic macular edema associated with severe capillary loss: one-year results of a pilot study. *Am J Ophthalmol*. 2009; 147(6):1022-30, 1030.
5. Avery RL1, Pearlman J, Pieramici DJ, Rabena MD, Castellarin AA, Nasir MA, et al. Intravitreal bevacizumab (Avastin) in the treatment of proliferative diabetic retinopathy. *Ophthalmology*. 2006; 113(10):1695.e1-15.

6. Glassman AR, Miller KM, Scott IU, Stockdale CR, Sun JK. Randomized Trial Evaluating Ranibizumab Plus Prompt or Deferred Laser or Triamcinolone Plus Prompt Laser for Diabetic Macular Edema .Ophthalmology. 2010; 117(6): 1064–1077.e35.
7. Fernando Arevalo J. Intravitreal Bevacizumab as Anti-Vascular Endothelial Growth Factor in the Management of Complications of Proliferative Diabetic Retinopathy. Med Hypothesis Discov Innov Ophthalmol. 2013 spring; 2(1):20-24.
8. Biester S, Ziemssen F, Ulrich Bartz-Schmidt K, Gelissen F. Is intravitreal bevacizumab treatment effective in diffuse diabetic macular edema? Graefes Arch Clin Exp Ophthalmol. 2009; 247(11):1575-7.
9. Simó R, Hernández C. Intravitreal anti-VEGF for diabetic retinopathy: hopes and fears for a new therapeutic strategy. Diabetologia. 2008 Sep; 51(9):1574-80.
10. Elie Dolgin, In vision trial, some researchers would rather see double. Nature Medicine. 2010; 16 (6) 611.
11. Nicholson BP, Schachat AP. A review of clinical trials of anti-VEGF agents for diabetic retinopathy. Graefes Arch Clin Exp Ophthalmol. 2010; 248(7):915-30.
12. Massin P, Bandello F, Garweg JG, Hansen LL, Harding SP, Larsen M ,et al. Safety and efficacy of ranibizumab in diabetic macular edema (RESOLVE Study): a 12-month, randomized, controlled, double-masked, multicenter phase II study. Diabetes Care. 2010; 33(11):2399-405.

13. Mitchell P, Bandello F, Schmidt-Erfurth U, Lang GE, Massin P, Schlingemann RO, et al. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. *Ophthalmology*. 2011; 118(4):615-25.
14. Stefanini FR, Badaró E, Falabella P, Koss M, Farah ME, Maia M. Anti-VEGF for the Management of Diabetic Macular Edema. *J Immunol Res*. 2014; 2014:632307.
15. Minnella AM, Savastano CM, Ziccardi L, Scupola A, Falsini B, Balestrazzi E. Intravitreal bevacizumab (Avastin) in proliferative diabetic retinopathy. *Acta Ophthalmol*. 2008; 86(6):683-7
16. Matsuda S, Tam T, Singh RP, Kaiser PK, Petkovsek D, Carneiro G, Zanella MT, Ehlers JP. The impact of metabolic parameters on clinical response to VEGF inhibitors for diabetic macular edema. *J Diabetes Complications*. 2014;28(2):166-70..
17. Ferenchak K, Duval R, Cohen JA, Maccumber MW. Intravitreal bevacizumab for postoperative recurrent vitreous hemorrhage after vitrectomy for proliferative diabetic retinopathy. *Retina*. 2014 Jan 22. [Epub ahead of print.

Table 1. Maximum, minimum, mean and median variables under study in the studied patients

Variable	No	Min	Max	Mean $\pm$ Sd	median
Age	30	39	83	60.47 $\pm$ 8.94	59.5
Duration of right eye F/U	17	3	32	11.94 $\pm$ 9.04	9
Duration of left eye F/U	26	3	36	14.23 $\pm$ 9.84	12
Number of injection on R E during M/FU	17	1	3	1.24 $\pm$ 0.56	1
Number of injection on L	26	1	2	1.23 $\pm$ 0.43	1

E during 26

M/FU

Diabetes	30	2	25	8.47 ± 5.28	7
duration					

F/U = Follow-up, LE = Left eye,R E = Right eye,M=Month

Figure 1. Visual outcome before and after of avastin injection.

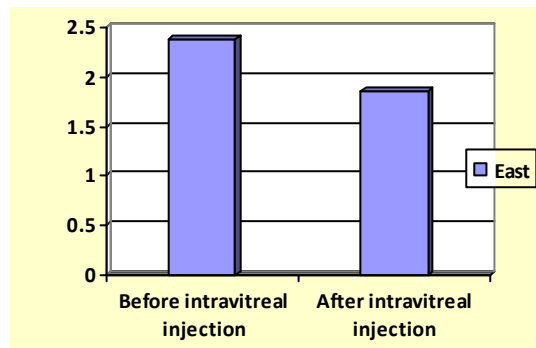


Table 2. Comparative study of visual acuity difference before and after intravitreal avastin injection according to diabetes duration and age.

	Diabetes duration		Age	
	Spirman	P-Value	Spirman	P-Value
Difference of VA of R eye (according to LOG-MAR)	-0.364	-0.048	0.230	0.222
Difference of VA of L eye (according to LOG-MAR)	-0.490	-0.006	0.021	0.913
VA= visual acuity, L = Left, R = Right, LOG-MAR = Logarythm of minimum angel resolution.				

Table. 3 Comparative study of visual acuity difference before and after intravitreal avastin injection according to right and left eye.

	Before avastin injection (according to LOG-MAR)	After avastin injection (according to LOG-MAR)	
	Mean $\pm$ SD	Mean $\pm$ SD	P-Value
VA of R eye	1.05 $\pm$ 1.04	0.83 $\pm$ 0.98	0.01
VA of L eye	1.34 $\pm$ 0.85	1.03 $\pm$ 0.80	0.02

VA= visual acuity, L = Left, R = Right, LOG-MAR = Logarithm of minimum angel resolution.

Figure legends:

Figure 2. A&B: Right and Left iris neovascularisation Date; 7/06/2009 .

, Date; 14/4/2010 C&D:Right and Left iris neovascularisation

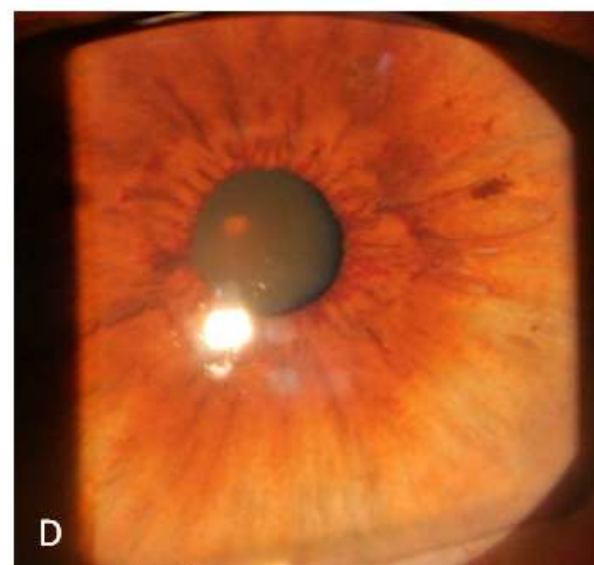
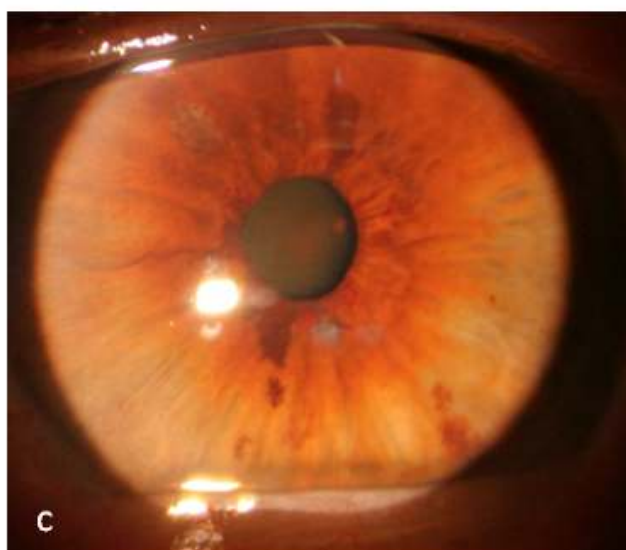
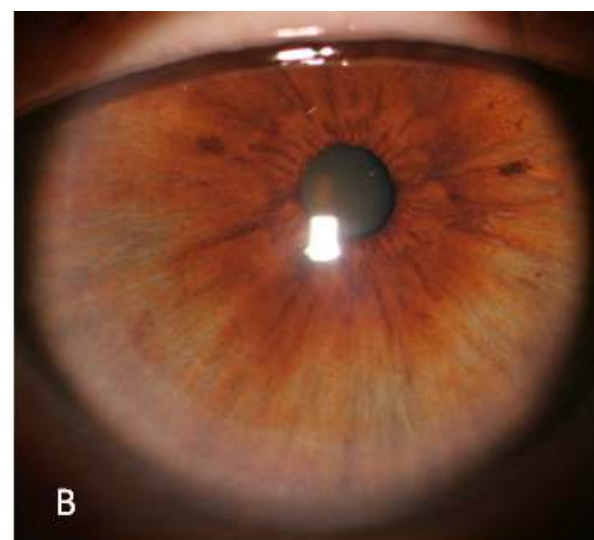
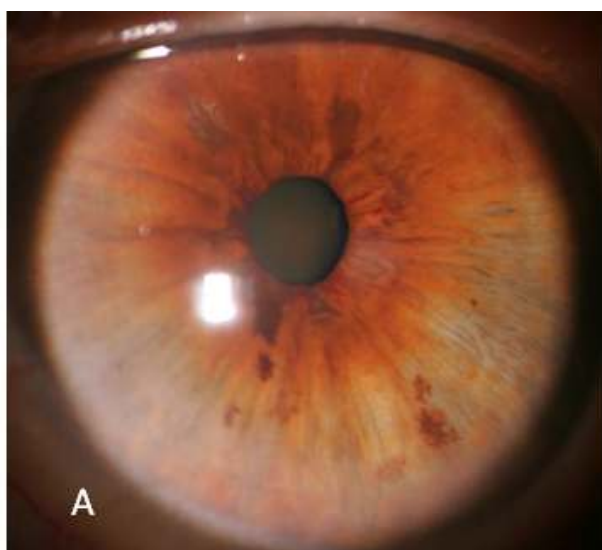


Figure 2. A&B: Right and Left iris neovascularisation Date; 7/06/2009 .
C&D:Right and Left iris neovascularisation , Date; 14/4/2010

Figure 3.A&B: Disappearance of Right iris neovascularisation Date; 0/6/2010, C Disappearance of Right iris neovascularisation and D reappearance of Left iris neovascularisation Date; 18/6/2011

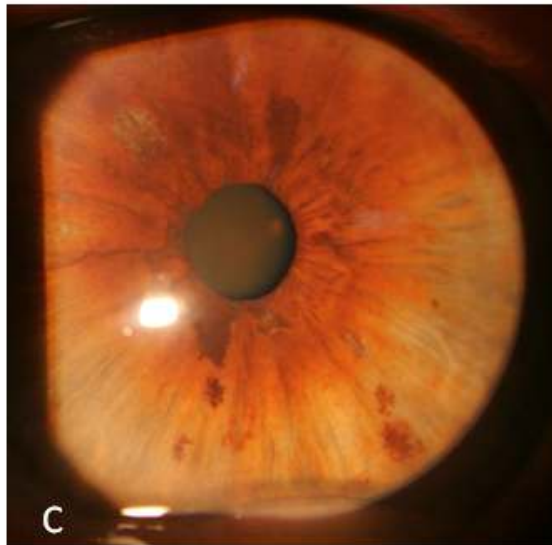
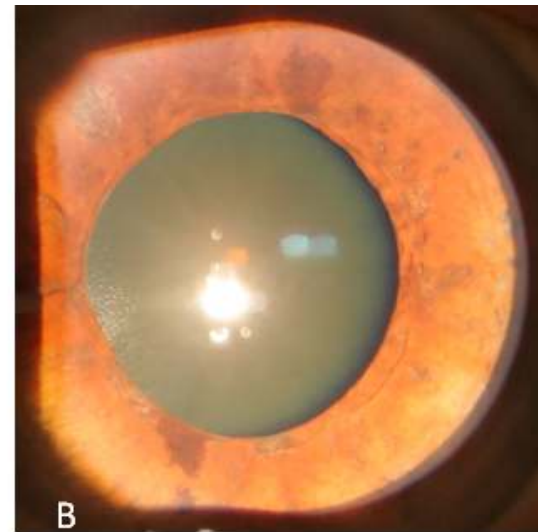
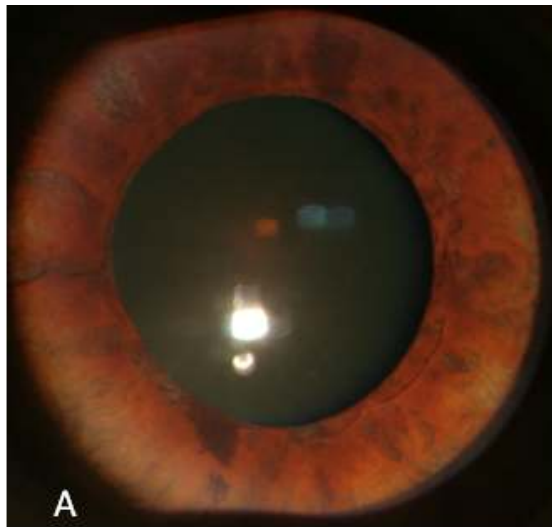


Figure 3. A&B: Disappearance of Right iris neovascularisation Date; 0/6/2010, C Disappearance of Right iris neovascularisation and D reappearance of Left iris neovascularisation Date; 18/6/2011