Bevacizumab for the Treatment of Macular Edema

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ABSTRACT

Background: anti-vascular endothelial growth factor (anti-VEGF) has been suggested for the treatment of macular edema. In this study we are assessing the efficacy of one type of anti-vascular endothelial growth factor which is Bevacizumab (Avastin) in the reduction of macular thickness.

Patients and Methods: from the period of February 2012 to February 2015, we have gathered the data of 54 patients (39=males, 15 =females) suffering from macular edema who received variable number of intraocular injections of Bevacizumab to be included in a retrospective study. One eye from each patient was chosen randomly and then we observe their follow-up Optical Coherence Tomography (OCT) for any changes in the thickness of the macula.

Results: after receiving a single Bevacizumab injection, 16 patients (29.6%) did not show any improvement while 22 (40.7%) patients show an improvement that was less than 50 microns of reduction in magnitude, 5 patients (9.2%) showed an improvement that was greater than 50 microns in reduction of macular thickness and the remaining 11 patients (20.3%) had a reduction of macular thickness that was greater than 100 microns.

Conclusion: despite being used originally for metastatic colon cancer, Bevacizumab (Avastin) can be used in the treatment of diabetic macular edema.

Keywords: diabetic retinopathy, Bevacizumab, intravitreal injection, macular edema, vascular endothelial growth factor.

INTRODUCTION

One of the most common disorders that the contemporary world population is suffering from is diabetes mellitus, with an estimated global prevalence of 9% among adults aged 18+ years [1]. Diabetes can be defined as a heterogeneous and complex disorder of the body metabolism characterized by high levels of glucose concentration in the blood [2]. Diabetes has a major impact on the body normal physiology and one of its complications is its effect on the body vasculature, especially the eye, where it causes the clinical condition of "diabetic retinopathy". Diabetic retinopathy has 4 main stages: mild, moderate and severe Non-Proliferative Diabetic Retinopathy (NPDR) followed by Proliferative Diabetic Retinopathy (PDR), and macular edema can develop in any of these stages [3].

Macular edema can be defined as: "retinal thickening within 2 disc diameters of the center of the macula, results from retinal microvascular changes that compromise the blood-retinal barrier, causing leakage of plasma constituents into the surrounding retina and, consequently, retinal edema" [4]. Macular edema is classified into 2 main categories: cystoid and diabetic macular edema [4].

The normal thickness of the macula is defined by two variables: foveal thickness and central foveal thickness, the normal foveal thickness in healthy eyes when measured by Optical Coherence Tomography (OCT) is 212±20 µm and the central foveal thickness is 182±23 µm [5]. Patients with macular edema suffer from blurry or wavy central vision, and their color perception may be disrupted [6]. The treatment of macular edema varies between different doctors. Three main treatment options were considered in the past [7]:

1- Focal laser treatment,
2- Non-steroidal anti-inflammatory drugs (NSAIDs) and Intravitreal implants.

As macular edema develops as a consequence of forming new, fragile and leaking blood vessels in the retina, that means if we stop the growth of these blood vessels the problem can be managed [8]. Following this hypothesis, anti-vascular endothelial growth factor (anti-VEGF) drugs were considered for treatment such as Bevacizumab (Avastin), Ranibizumab (Lucentis) and Pegaptanib (Macugen) [8]. The purpose of this study is to observe and assess one kind of anti-VEGF which is Bevacizumab (Avastin) and its efficacy in reducing the formation of new, fragile and leaking blood vessels, by inhibiting vascular endothelial growth factor (produced in response to ischaemia) binding to endothelial cells [9] and hence, treating macular edema.

MATERIALS AND METHODS
Study design

This is a retrospective randomized study designed to monitor the effect of Bevacizumab in patients suffering from macular edema post treatment with intraocular injections and record the results based on their follow-up Optical Coherence Tomography scan and the percentage of improvement (if the patient has improved).

Participants

We have gathered the data of 54 patients with macular edema (39=males, 15=females) who received intraocular Bevacizumab injections aged between 30 and 90 years old from the period of February 2012 to February 2015. The range of the sample =707 microns, the sample variance=24978.04, standard deviation=158.04 microns.

Choice of the eye

If a patient was suffering from macular edema in both of his/her eyes, and received Bevacizumab injection in both of them.

Delivery of the drug

Anti-VEGF drugs are delivered as intraocular injections. Every injection has a dose of 0.05 ml of 2 mg of Bevacizumab.

Number of injections

Different patients received different number of injections, 40 of the cases received only one injection, while the remaining 14 of the cases received multiple injections with a period of 4 to 6 weeks interval between any two injections (Table 2 and 3 in the appendix).

Optical Coherence Tomography scan

After each injection an Optical Coherence Tomography scan is carried after 4 weeks of the time of the injection to monitor any positive or negative findings regarding the reduction in the thickness of the macula and results (whether there is any improvement or not) are recorded. An optical coherence tomography is a non-invasive way to measure the thickness of the macula where the instrument takes multiple slices of the macula and record the thickness of every single one of them in microns. In this study we are focusing specially on central subfoveal mean thickness (CSMT) which is the 1 mm diameter circular area shown in the thickness map when reviewing the results of the scan. This area has a higher reproducibility and stronger correlation compared to the other areas of the macula [10]. The device was manufactured by Heidelberg Engineering.

Percentage of improvement

After we gathered the data of our patients from the optical coherence tomography device, we compared the initial macular thickness with the follow-up macular thickness in patients who had reduction in thickness to obtain the net difference between the two, after that we divided the difference on the initial thickness and multiplied it by 100 to obtain the percentage of improvement. And in the case of multiple injections we added up the differences between the pre- and post-injections optical coherence tomography in patients who showed continuous reduction after each injections and we divided them by the first scan thickness and multiplied it by 100.

Significant and non-significant improvement

In the present study, we used the Diabetic Retinopathy Clinical Research Network (DRCRnet) standards to determine whether an improvement is significant or not. The Diabetic Retinopathy Clinical Research Network states that any improvement greater than 11% in magnitude in the reduction of central subfoveal mean thickness is likely to be significant[11].

The study was done after approval of ethical board of King Abdulaziz university.

RESULTS
Single Injection Optical Coherence Tomography

Out of the 54 patients, after receiving a single Bevacizumab injection, 16 patients (29.6%) did not show any improvement and their macula became more edematous. However, 22 (40.7%) patients showed an improvement and thinning of the macula that was less than 50 microns in magnitude, 5 patients (9.2%) showed an improvement that was greater than 50 microns in reduction of macular thickness and the remaining 11 patients (20.4%) had a reduction of macular thickness that was greater than 100 microns (p=0.00001) (95% CI =32.9) Table 1.

Table 1: Net improvement/reduction of macular thickness in the enrolled patients after single Bevacizumab injection

No of Patients	Net improvement in microns	%
16	No improvement	27.6%
22	0 – 49	40.7%
5	50 – 99	9.3%
11	≥ 100	20.4%

Multiple Injections Optical Coherence Tomography

14 patient took a multiple course of Bevacizumab injections, only one patients did not improve and his macula became thicker following every injection, and three patients did not improve at the first injection and afterwards their macula became thinner with the second injection, 5 patients showed continuous positive results and 5 patients had and improve-relapse episode.

Single Injection Improvement Percentage

Based on our data obtained from the Optical Coherence Tomography device, 21 patients (38.8% of the total number of patients who received the single injection), had a percentage of improvement that was greater than 11%, while the remaining 17 patients (31.4%) showed an improvement that was less than 11% in relation to their baseline macular thickness.

Multiple injections improvement percentage

5 patients out of 14 showed continuous positive results following each injection with Bevacizumab, and the percentage of improvement where: 29.6%, 4.6%, 9.8%, 83% and 15%.

DISCUSSION

On summary of the results, patients who received a single Bevacizumab injection did not show one main result, instead they were divided into 3 main thirds with the majority of patients showing an improvement with the biggest percentage (38.8%) showing a significant improvement in the reduction of thickness of their macula. On the other hand, nearly half of the patients who had multiple Bevacizumab injections showed eventual positive results, and nearly the other half had progressed at first but then had a relapse episode.
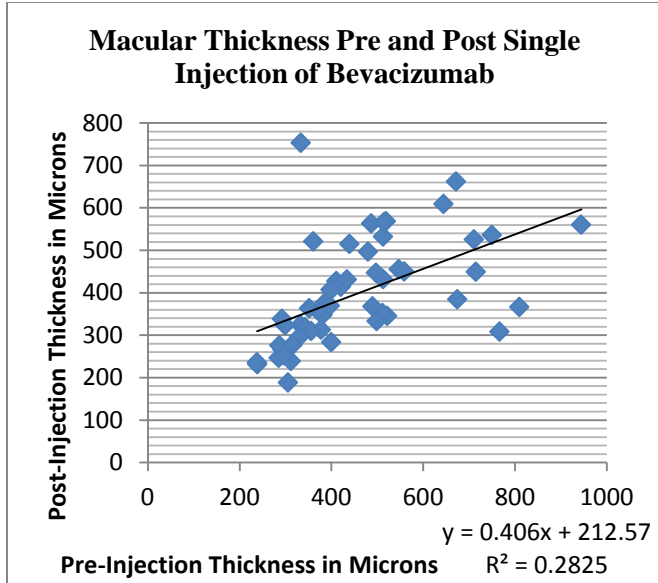
Macular Thickness Pre and Post Single Injection of Bevacizumab

$y = 0.406x + 212.57$

$R^2 = 0.2825$

Figure 1: Effect of Single Bevacizumab injection on macular thickness

R^2 =coefficient of détermination

Based on the findings that we obtained from the study, and despite the 16 patients who did not respond to the drug, generally Bevacizumab showed its ability to reduce macular thickness considerably in the majority of patients and hence improving their vision.
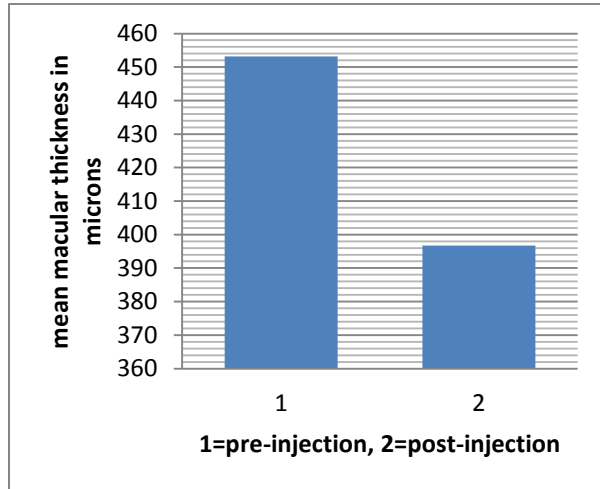
Figure 2: Effect of Bevacizumab injection on macular thickness (difference between macular thickness in the pre-injection and post-injection of Bevacizumab)

Another issue that should be discussed is the use of multiple Bevacizumab injection in the treatment of macular edema. From the data we gathered in the study, in many cases a single intraocular injection was not sufficient to restore the normal thickness of the macula. Although the data collected in this study for patient who received multiple injections is not sufficient, but it is capable of raising the issue of Bevacizumab showing significant improvement in vision in the long term when used repeatedly, 8 out of the 14 patient showed eventual positive results and continuous thinning of the macula.

Bevacizumab is not the only drug prescribed by doctors to treat macular edema, in fact, bevacizumab is used as an "off-label" drug when used in the eye, and Bevacizumab was originally developed to treat specific types of cancer such as metastatic colon cancer. The FDA approved drug to treat macular edema is actually Ranibizumab (Lucentis). Many doctors and researchers claim that Ranibizumab is a better choice when it comes to the eye, and Ranibizumab was fully tested as a treatment for macular problems, but no studies have been completed to compare the two drugs [12].

We should not forget also the financial aspects of the two treatments, many ophthalmologists still prescribe Bevacizumab over Ranibizumab because of the vast difference in price between the two, where Bevacizumab cost only 1-3% of Ranibizumab cost [13]. Although it may not be as efficient as Ranibizumab, Bevacizumab was able to reduce macular thickness efficiently in many cases and it is more economically convenient for patients without health insurance [13].

Another issue that can be discussed is the safety of using intraocular Bevacizumab in treatment of eye conditions, the use of Bevacizumab in the treatment of colon cancer reported an increase in thromboembolic events in a meta-analysis of several trials from 1.9% to 4.4%, while no definitive information and side effects were reported in the short term when used as an

intraocular injection for the treatment of eye disease [14].

In conclusion, Bevacizumab showed its efficacy and ability to manage macular edema when used as a single or multiple intraocular injections.

REFERENCES

1. **World Health Organization (2011):** Diabetes. Fact sheet N 312, Available at: http://www.who.int/mediacentre/factsheets/fs312/en/.

2. **Triplitt C, Solis-Herrera C, Reasner C, DeFronzo RA, Cersosimo E (2015):** Classification of Diabetes Mellitus. Endotext [Internet], available at: http://www.ncbi.nlm.nih.gov/books/NBK279119/

3. **National Eye Institute(2015):** Facts About Diabetic Eye Disease. https://www.nei.nih.gov/health/diabetic/retinopathy

4. **Mavrikakis E, Khan BU, Lam W (2015):** Macular edema in diabetes. Medscape,30.

5. **Chan, Annie Duker, Jay S Ko, Tony H Fujimoto, James G Schuman, Joel S (2006):** Normal macular thickness measurements in healthy eyes using Stratus optical coherence tomography. Archives of ophthalmology, 124(2):193-8.

6. **Cleveland Clinic. Cystoid Macular Edema(2015):** http://my.clevelandclinic.org/services/cole-eye/diseases-conditions/hic-cystoid-macular-edema.

7. **Ford JA, Lois N, Royle P, Clar C, Shyangdan D, Waugh N (2013):** Current treatments in diabetic macular oedema: systematic review and meta-analysis. BMJ., 3(3):e002269.

8. **Virgili G, Parravano M, Evans JR, Gordon I, Lucenteforte E (2017**): Anti-vascular endothelial growth factor (anti-VEGF) drugs for diabetic macular oedema: a network meta-analysis. The Cochrane Library, available at : http://onlinelibrary.wiley.com/getIdentityKey?redirectTo=http%3A%2F%2Fonlinelibrary.wiley.com%2Fdoi%2F10.1002%2F14651858.CD007419.pub5%2Ffull%3Fwol1URL%3D%2Fdoi%2F10.1002%2F14651858.CD007419.pub5%2Ffull&userIp=41.47.38.17&doi=10.1002%2F14651858.CD007419.pub5

9. **EyeWiki. Bevacizumab(2015):** http://eyewiki.aao.org/Bevacizumab

10. **The Foundation of The American Academy of Opthalmology(2015):** http://www.aao.org/yo/newsletter/201005/article05.cfm

11. **Wykoff CC, Hariprasad SM (2016) :** DRCR Protocol-T: Reconciling 1- and 2-Year Data for Managing Diabetic Macular Edema. PubMed., 47(4):308-12.

12. **Fong AH, Lai TY (2013):** Long-term effectiveness of ranibizumab for age-related macular degeneration and diabetic macular edema. Clinical interventions in aging, 8:467.

13. **Steinbrook R (2006):** The price of sight - ranibizumab, bevacizumab, and the treatment of macular degeneration. N Engl J Med., 355(14):1409–1412.

14. **Michels S (2006):** Is intravitreal bevacizumab (Avastin) safe? British Journal of Opthalmology, 90(11): 133-1334.

15. **Yuan A, Ahmad BU** *et al.* **(2014) :** Comparison of intravitreal ranibizumab and bevacizumab for the treatment of macular edema secondary to retinal vein occlusion. International journal of ophthalmology, 7(1):86.