Cover Page

Evaluation of the Effect of Intravitreal Injections of Anti-VEGF on Macular Perfusion in Diabetic Patients Using OCTA (IMPACT)

NCT03246152

Upload date: 12/25/2019
Review date: 4/3/2017

Faculty of Medicine, Cairo University Postgraduate Research Program Template

1. Proposed Study Title

Evaluation of the effect of repeated intravitreal injections of Anti-VEGF on macular perfusion in diabetic patients using optical coherence tomography angiography

2. Background and Rationale

Over the past few years, anti-vascular endothelial growth factor (VEGF) drugs have become the mainstay of therapy for diabetic macular edema (DME), substantially improving visual acuity for many diabetics worldwide, and proving effective for treatment of both non-proliferative and proliferative diabetic retinopathy.[1]

The Early Treatment Diabetic Retinopathy Study (ETDRS) group founded guidelines for treating patients with clinically significant DME (CSME) with focal/grid macular laser photocoagulation.[2] Since then, macular laser, and steroids, were the main therapies for treatment of DME until anti VEGF drugs were developed after a growing body of scientific evidence implicated VEGF in the pathophysiologic process of DME.[3,4]

Several explanations are present for how VEGF results in the dysfunction of the blood–retinal barrier in patients with DME, including (1) being an important mediator for several proinflammatory mediators in diabetic retinopathy (e.g. cytokines); (2) the direct effects on tight junction-associated proteins (as B-catenin and occludin); and (3) induction of pericyte degeneration and depletion.[5]

Many studies such as Diabetic Retinopathy Clinical Research [DRCR] Network studies, RESTORE Study,[6] RISE and RIDE Research Group,[7] and The BOLT Study[8] have supported the use of anti-VEGF agents in the treatment of DME with better visual outcomes using anti-VEGF injections alone or in combination with other treatments.

One of these studies, The BOLT study, compared ETDRS macular laser treatment (MLT) to intravitreal bevacizumab in patients with persistent CSME. After 2 years, the bevacizumab group had a median of 9 letters gained, compared to 2.5 letters for the MLT group ($p = 0.005$).[8]

Several ocular complications of intravitreal anti-VEGF injections have been reported including endophthalmitis, cataract and retinal detachment. The effect of anti-VEGF drugs on macular perfusion has been inconclusive, with mixed reports of increase, decrease or no effect on perfusion in response to anti-VEGF treatment. In

many of these studies, however, patients with more ischaemic retinas were not included.[8,9] Retinal ischemia is an important factor in the progression and prognosis of diabetic retinopathy.

Some studies showed sustained retinal arteriolar vasoconstriction in eyes treated with anti-VEGF,[10] while others demonstrated using ultrasound decreased blood flow velocities in all retrobulbar arteries after intravitreal anti-VEGF injections.[11] This could indicate that anti-VEGF agents may have an effect on the ocular perfusion.

Fluorescein angiography (FA) was the method used to assess changes in macular perfusion after anti-VEGF injections in most of the studies.[6,7,8] Despite its clinical usefulness, however, FA is known to have documented risks.[12] Optical coherence tomography angiography (OCTA) is a new noninvasive method of acquiring high-resolution images of the retinal vasculature that can be utilized in the treatment of retinal disease without the need for dye injection. It allows the visualization of both the superficial and deep retinal capillary layers separately and the construction of microvascular flow maps. [13]

OCTA uses high-speed OCT scanning to detect the flow of blood by analyzing signal decorrelation between two sequential OCT cross-sectional scans repeated at the same location. Because of the movement of erythrocytes within a vessel, compared to stationary areas of the surrounding retina, only perfused blood vessels will result in signal decorrelation, leading to their imaging. The split-spectrum amplitude decorrelation angiography (SSADA) algorithm improves the signal to noise ratio.[14]

Several studies have proved the reliability of OCTA in detecting and quantifying macular ischemia in diabetics.[14,15,16]

In our study, we aim to evaluate the effect of repeated intravitreal injections of Anti-VEGF on the perfusion of different capillary layers in the macula of diabetic patients using OCTA.

3. Objectives

To study the effect of repeated intravitreal injections of Anti-VEGF on macular perfusion in diabetic patients using optical coherence tomography angiography

4. Study Design

Prospective interventional study

5. **Ethical committee approval**: Yes

6. **Study Methods**

Type 1 and 2 diabetic patients requiring intravitreal Anti-VEGF injections for treatment of center involving diabetic macular edema

Inclusion criteria:

1) Patients ≥ 18 years old with type 1 or 2 diabetes mellitus with decreased BCVA due to diabetic macular edema and center involvement by the edema on spectral domain optical coherence tomography (SD OCT) with any stage of diabetic retinopathy

Exclusion criteria:

1) Ocular conditions that may affect macular perfusion (e.g. retinal vascular diseases, uveitis, vasculitis etc.)
2) History of vitreoretinal surgeries (excluding intravitreal injections)
3) Any previous treatment for diabetic macular edema
4) Presence of epiretinal membrane involving the macula or vitreomacular traction
5) Media opacity preventing good image quality
6) Uncontrolled glaucoma
7) Thromboembolic events within 6 months

Methodology in details

This is a prospective interventional study to evaluate the effect of repeated intravitreal injections of Anti-VEGF on macular perfusion in diabetic patients using optical coherence tomography angiography (OCTA).

Each patient will receive a detailed ophthalmologic examination including measurement of BCVA as well as applanation tonometry, undilated and dilated slit-lamp biomicroscopic examination and indirect fundus examination.

Duration of diabetes and its control through HbA1C measurement will be recorded for each patient.

Type 1 and 2 diabetic patients found to have BCVA worse than 6/6 and

clinical evidence of macular edema will undergo SD OCT and FA.

Patients with center involved macula edema detected by SD OCT will be included in the study and will undergo baseline macular OCTA.

These patients will then undergo intravitreal injections of Anti-VEGF monthly for 3 months then OCTA will be repeated to evaluate changes in macular perfusion and SD OCT will be repeated to assess retinal thickness. Patients with center involving macular edema on SD-OCT after the first 3 injections will continue to receive intravitreal Anti-VEGF injections monthly until the edema subsides or the study duration ends. These patients then undergo a final macular OCTA for perfusion evaluation and SD OCT for thickness assessment.

OCTA will be performed with an Avanti RTVue XR system (Optovue, Inc., Fremont, CA, USA). Area of FAZ and capillary density at each capillary layer will be calculated before and after interventions using the OCTA machine software and ImageJ software.

All statistical analyses will be done using IBM SPSS v20.0 statistical software (IBM Corporation, NY, USA). Descriptive statistics will be calculated, and the data will be summarized as mean ± SD for numerical data, and as frequencies and percentages for categorical data.

Possible Risk (mention if there is any risk or not)

Risk of cataract, glaucoma, endophthalmitis, retinal detachment, central retinal artery occlusion and vitreous hemorrhage

Primary outcomes

1- Effect of repeated intravitreal Anti-VEGF injections on Foveal Avascular Zone (FAZ) area and capillary density as a measure of macular perfusion change at different capillary levels in the macula.

Secondary outcome parameters

1- Effect of intravitreal Anti-VEGF injections on microaneurysms and vascular changes in the superficial and deep capillary plexuses of the macula using OCTA

2- Effect of intravitreal Anti-VEGF injections on choriocapillaris density using OCTA

3- Correlation of BCVA with degree of capillary non-perfusion before and after injections

Sample size (number of participants included)

50 eyes

Source of funding (is there any source of funds or not)

Self

7. Time plan

6 months from first injection

References:

1. Radwan S. Ajlan, Paolo S. Silva & Jennifer K. Sun (2016) Vascular Endothelial Growth Factor and Diabetic Retinal Disease, Seminars in Ophthalmology, 31:1-2, 40-48, DOI: 10.3109/08820538.2015.1114833
2. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema: Early Treatment Diabetic Retinopathy Study report number 1. Arch Ophthalmol 1985; 103:1796–806.
3. Regression of retinal and iris neovascularization after intravitreal bevacizumab (Avastin) treatment. Retina 2006; 26:352– 4.
4. Pegaptanib: a novel approach to ocular neovascularization. Ann Pharmacother 2006;40:1322– 6.
5. Zhang X, Bao S, Hambly BD, et al. Vascular endothelial growth factor-A: A multifunctional molecular player in diabetic retinopathy. Int J Biochem Cell Biol 2009;41: 2368–2371.
6. Mitchell P, Bandello F, Schmidt-Erfurth U; et al. RESTORE Study Group. The RESTORE Study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmology 2011; 118:615–25
7. Nguyen QD, Brown DM, Marcus DM, et al. RISE and RIDE Research Group. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology 2012;119:789–801.
8. Michaelides M, Kaines A, Hamilton RD. 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; 117:1078–1086
9. Manousaridis K, Talks J. Macular ischaemia: a contraindication for anti-VEGF treatment in retinal vascular disease? Br J Ophthalmol 2012;96(2):179-84.
10. Papadopoulou DN, Mendrinos E, Mangioris G, Donati G, Pournaras CJ. Intravitreal ranibizumab may induce retinal arteriolar vasoconstriction in patients with neovascular age-related macular degeneration. Ophthalmology 2009; 116(9): 1755–1761.
11. Bonnin P, Pournaras JA, Lazrak Z, et al. Ultrasound assessment of short term ocular vascular effects of intravitreal injection of bevacizumab

(Avastin((R))) in neovascular age-related macular degeneration. Acta Ophthalmol 2010;88: 641–645.
12. Yannuzzi LA, Rohrer KT, Tindel LJ, et al. Fluorescein angiography complication survey. Ophthalmology. 1986;93: 611–617.
13. Spaide RF, Klancnik JM Jr, Cooney MJ. Retinal vascular layers imaged by fluorescein angiography and optical coherence tomography angiography. JAMA Ophthalmol. 2015;133:45–50.
14. Freiberg, F.J., Pfau, M., Wons, J. et al, Optical coherence tomography angiography of the foveal avascular zone in diabetic retinopathy. Graefes Arch Clin Exp Ophthalmol. 2016;254:1051–1058.
15. Bradley PD, Sim DA, Keane PA, et al. The evaluation of diabetic macular ischemia using optical coherence tomography angiography. Invest Ophthalmol Vis Sci. 2016;57(2):626–631.
16. Hwang TS, Gao SS, Liu L, et al. Automated quantification of capillary nonperfusion using optical coherence tomography angiography in diabetic retinopathy. JAMA Ophthalmol. 2016;134(4):367–373.