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Case Report	:	Intravitreal Bevacizumab Injection for Neovascular Age-Related Macular Degeneration; Review of Five Cases
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Intravitreal Bevacizumab Injection for Neovascular Age-Related Macular Degeneration; Review of Five Cases

Abstract

Introduction: Age-related macular degeneration (AMD) is the leading cause of blindness in the developed world in people over 50-years-old. Research shows that with anti-vascular endothelial therapy (anti-VEGF) vision loss can be avoided in over 90% of patients with neovascular AMD. Off-label intravitreal bevacizumab exhibited comparable efficacy to other anti-VEGF therapy.

Purpose: To review five cases of neovascular AMD who got intravitreal bevacizumab injection at Cicendo National Eye Hospital.

Case report: Case one, a 69-years-old female with AMD AREDS IV on both eyes with vitreous hemorrhage on left eye (LE) and vitrectomized eye of LE. Patient underwent five bevacizumab injection on her right eye (RE). Final visual acuity (VA) was improve than baseline VA. Case two, a 60-years-old female with AMD AREDS II RE and AMD AREDS IV LE. Patient underwent eigth bevacizumab injection on LE. Final VA was lower than baseline VA. Case three, a 69-years-old male, with AMD AREDS IV on both eyes. Patient underwent six bevacizumab injection on RE and five injection on LE. Final VA of both eyes was improve than baseline VA. Case four, a 61-years-old female with AMD AREDS IV RE and epiretinal membrane LE. Patient underwent six bevacizumab injection on RE. Final VA was improve than baseline VA. Case five, a 62-years-old male with AMD AREDS IV RE and pseudophakia LE. Patient underwent five bevacizumab injection on RE. Final VA was improve than baseline VA.

Conclusion: Optimal management of neovascular AMD including evaluation and control of risk factors, timely injection of anti-VEGF according to disease activity and continuing education to patient itself. Off label intravitreal bevacizumab is efficient and safety option to reduce the financial burden over multiple injections.

Keywords: age-related macular degeneration, wet AMD, neovascular AMD bevacizumab, anti-VEGF

I. Introduction

Age-related macular degeneration (AMD) is the leading cause of blindness in the developed world in people over 50 years. Only about 10% of patients with AMD have the neovascular form, but it caused 90% of blindness related to AMD. The recent development of anti-vascular endothelial growth factor (anti-VEGF) agents has revolutionized therapy for this condition, and vision loss can now be avoided in over 90% of patients with neovascular AMD (AMD AREDS IV) with about one-third of patients experiencing significant improvements in visual acuity. However

there are two major barriers to the delivery of health care to this group of patients. The first is the cost and the second is the requirement to be seen monthly.[1-3]

Since the introduction of intravitreal bevacizumab therapy in 2005, this medication has been frequently used by retina specialists as an off-label treatment for AMD AREDS IV. Bevacizumab exhibited comparable efficacy to other anti-VEGF therapies (e.g., ranibizumab) in numerous trials conducted worldwide. Off-label intravitreal bevacizumab was found to be highly cost-effective compared with ranibizumab.[4-6]

This is a serial case of five patients with AMD AREDS IV who got more than or equal to five intravitreal bevacizumab injection in Cicendo Eye Hospital from January 2019 to December 2020.

II. Serial Case

2.1. Case One

A 69-years-old-female came to Cicendo National Eye Hospital on January 7th 2019 with chief complaint of gradually decreased vision on her left eye (LE) since 9 months ago. No history of red eye, eye pain or trauma. Patient had history of hypertension since one year ago but not routine take antihypertensive medication. There is no information about smoking history. Patient had history of LE pars plana vitrectomy with endolaser with gas tamponade on September 25th 2018 because of vitreous hemorrhage.

Patient's general examination was within normal limit. Ophthalmologic examination revealed the uncorrected visual acuity (UCVA) was 1/60 on right eye (RE) and 0.08 on LE. Ocular motility were full and intraocular pressure (IOP) in normal limit. Both lens were cloudy. Another anterior segment examination were in normal limit. Funduscopic examination of RE revealed subretina fibrosis and there is vitreous hemorrhage on LE. Patient was diagnosed with AMD AREDS IV on both eyes with vitreous hemorrhage on LE, vitrectomized eye of LE and immature senile cataract on both eyes and hypertension, with differential diagnosed with idiopathic polypoidal choroidal vasculopathy (IPCV) RE.

OCT examination on January 7th 2019 showed macular edema, irregularity of retinal pigment epithelium (RPE), and submacular hyperreflectivity material (SMHRM) on RE. On LE macular OCT revealed the intraretinal fluid. Patient underwent RE intravitreal anti-VEGF injection using bevacizumab on January 15th 2019, April 15th 2019 and June 13th 2019. On June 17th 2019, the UCVA RE were 0.2 and LE were hand movement because of vitreous hemorrhage. Patient underwent LE fluid air exchange on September 6th 2019. Patient underwent 4th and 5th RE bevacizumab injection on July 11th 2019 and August 12th 2019. Patient last visite was on december 11th 2019 with UCVA RE were 0.4 and LE was hand movement because of recurrent vitreous hemorrhage.

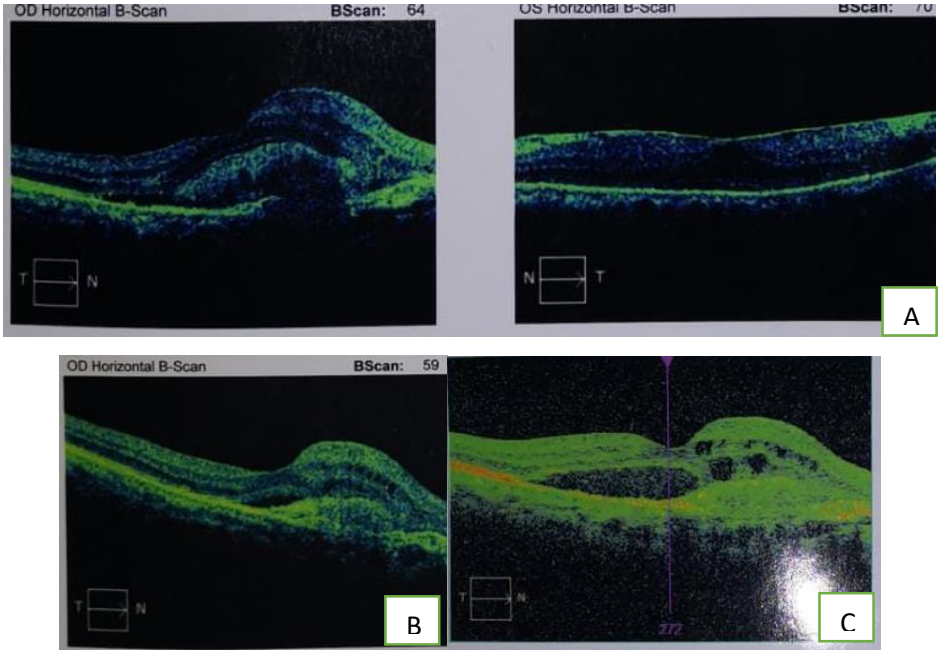

Figure 2.1. Patient's macular OCT A) January 7th 2019 (RE AND LE), B) June 20th 2019 (RE), C) November 5th 2019 (RE)

2.2. Case Two

A 60-years-old-female came to Cicendo National Eye Hospital on June 19th 2020 with chief complaint of gradually decreased vision on her LE since six months ago. No history of red eye, eye pain or trauma. Patient had history of hypertension for one year. No data about antihypertensive therapy. There is no information about smoking history.

Patient's general examination was within normal limit. Ophthalmologic examination revealed the UCVA was 1.0 on RE and 0.05 LE, full ocular motility and normal IOP. The lens were cloudy on both eyes. Another anterior segment examination was within normal limit. Funduscopic examination of RE revealed drusen in macula area, and there is drusen in macula and submacular hemorrhage in LE. Patient was diagnosed with AMD AREDS II RE, AMD AREDS IV LE and immature senile cataract RE and LE and hypertension. There is no data about preinjection OCT but there is consistent finding of SMHRM in each follow up OCT of LE.

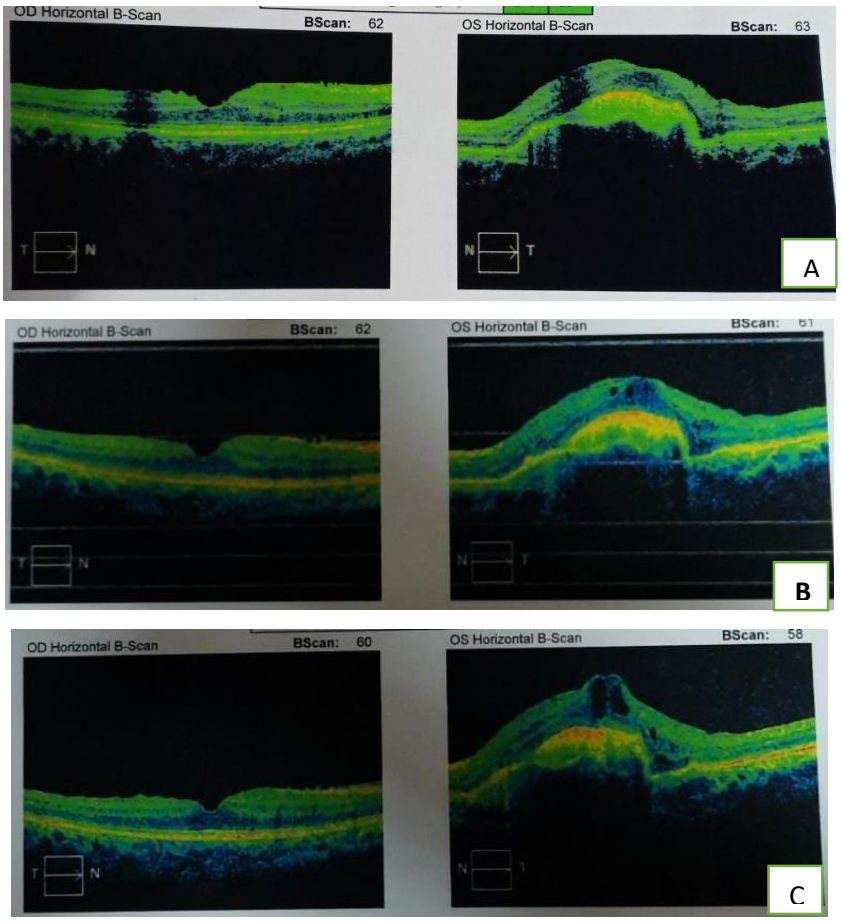

Figure 2.2. Patient's macular OCT A) October 21st 2019, B) February 17st 2020, C) June 17st 2020

Patient underwent intravitreal bevacizumab injection eight times in her LE. After 3 loading dose on July 10th 2019, August 9th 2019, October 14th 2019, UCVA

LE still the same. OCT examination was taken 1 week later. Next bevacizumab injection were scheduled at November 19th 2019 and Januari 20th 2020, then patient underwent macular OCT examination on February 2020 when UCVA LE were 0.1 The 6th bevacizumab injection were given at March 11th 2020. One week later UCVA were 2/60 and posterior segment examination show submacular fibrosis. OCT examination then taken again at march and april 2020 with similar findings like previous OCT. Patient underwent 7th and 8th bevazimab injection at June 19th 2020 and August 7th 2020. On follow up visit one week later UCVA RE 0.63, LE 1/60, and LE posterior segment examination showed submacular fibrosis. Bevacizumab injection were stopped and planned for conservative management of LE.

2.3. Case Three

A 69-years-old-male came to Cicendo National Eye Hospital on June 19th 2020 with chief complaint of gradually decreased vision on both eye since 1 week ago. No history of red eye, eye pain or trauma. Patient had no history of hypertension and diabetes. There is no information about smoking history.

Patient's general examination was within normal limit. Ophthalmologic examination revelaed the VA with patient's own spectacle correction were 0.4 on RE and 0.2 on LE, with full ocular motility and normal IOP. Lens were cloudy in both eyes. Another anterior segment examination were in normal limit. Funduscopic examination RE revealed macular drusen, and there is submacula fibrosis on LE. Patient was diagnosed with AMD AREDS IV on both eyes.

Patient underwent intravitreal bevacizumab injection six times in her RE and 5 times on LE. After 3 loading dose of intravitreal bevacizumab on RE at Januari 4th 2019, February 8th 2019, and March 15th 2019, VA RE were 1.0F on march 22th 2019. OCT taken and patient was given another dose of ranibizumab on April 26th 2019, then on June 21st 2019, with final UCVA RE were 0.8. Patient got another dose at February 21st 2020 with UCVA 1 week post injection 0.25.

In other hand, after three intravitreal bevacizumab injection on February 19th 2019, June 21st 2019, and August 23rd 2019, VA LE improved to 0.63 (with

patient's own spectacle correction). The fourth dose were October 10th 2019 and last dose in January 3rd 2020 with final UCVA LE after fifth dose were 0.4 (with patient's own spectacle correction). Patients then lost to follow up on march 2020.

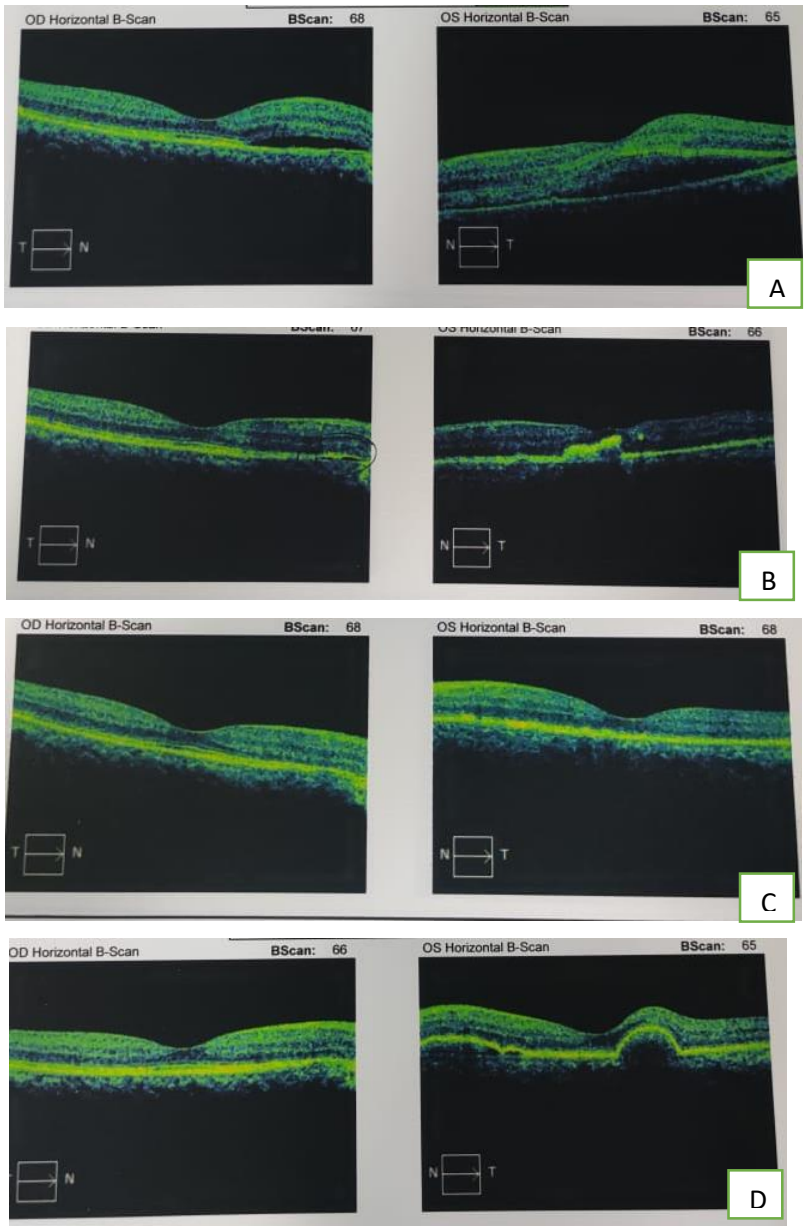

Figure 2.3. Patient's macular OCT A) January 3rd 2019, B) March 22nd 2019 C) May 16th 2019, D) February 2nd 2020

2.4. Case Four

A 61-years-old-female came to hospital on June 13th 2019 with chief complaint of sudden blurred vision on RE since 1 month ago. No history of red eye, eye pain, floaters, fotopsia, or trauma. Patient had no history of hypertension and diabetes. There is no information about smoking history.

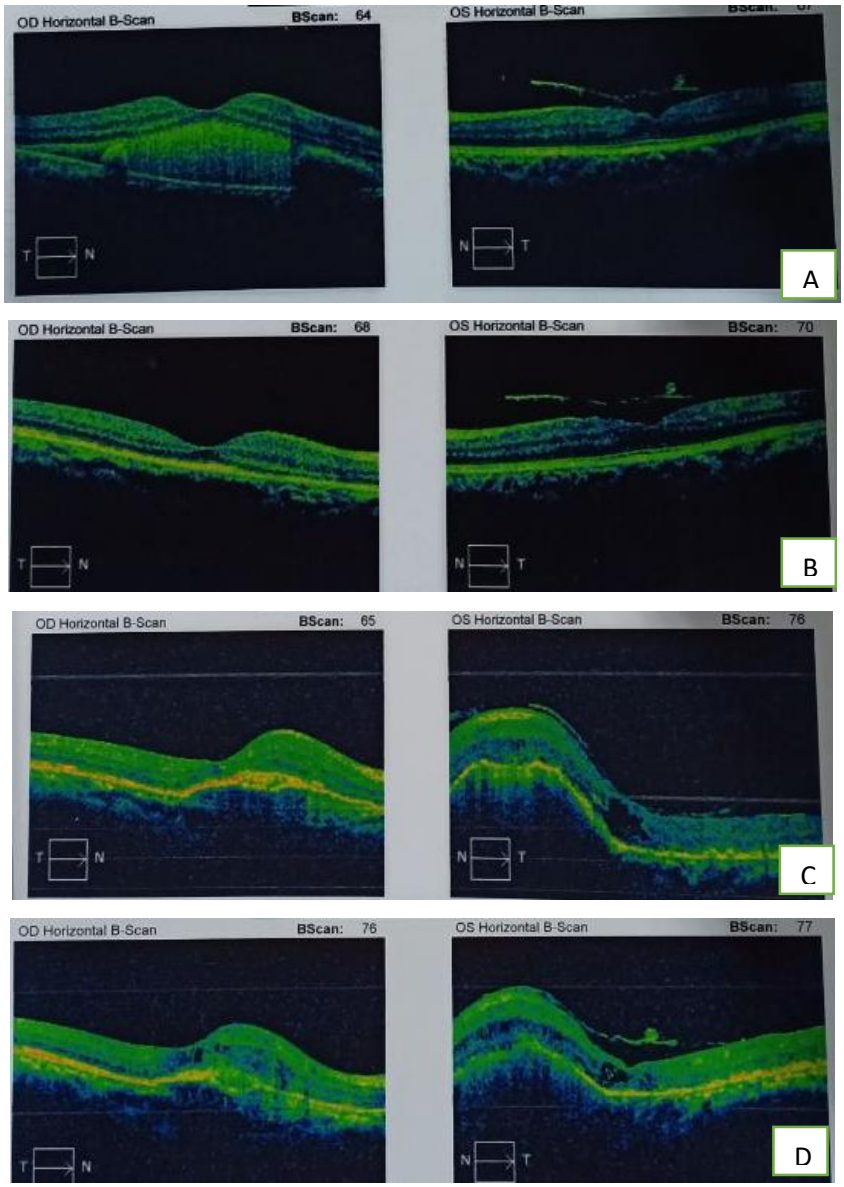

Figure 2.4. Patient's macular OCT A) June 13th 2019, B) August 22nd 2019, C) February 28th 2020 D) July 28th 2020

Patient's general examination was within normal limit. Ophthalmologic examination revelaed the UCVA were 0.16 on RE and 0.4 on LE, with full ocular motility and normal IOP. Both lens were cloudy. Another anterior segment examination were in normal limit. Funduscopic examination RE revealed submacular hemorrhage. Posterior segment of LE were in normal limit. OCT were taken. Patient diagnosed with submacular hemorrhage RE et causa AMD AREDS IV, epiretinal membrane LE and immature senile cataract on both eyes.

Patient got total six injection of bevacizumab on her RE. The loading dose was on July 3rd 2019, August 2nd 2019, and October 28st 2019. At one week follow up after 2nd injection, RE UCVA were 0.125. But when the patient got 3rd injection at October, RE UCVA were 4/60. On follow up January 2nd 2020, RE UCVA were 0.16. But then at June 5th 2020 RE UCVA were 0.2. Patient got his 4th injection that continue with 5th injection on July 17th 2020 and 6th injection at August 7th 2020. One week later final UCVA was 0.25 with submacular fibrosis on RE fundus examination. Patient then planned to continue her follow up at secondary health service.

2.5. Case Five

A 62-years-old-male came to hospital on January 1st 2019 with chief complaint of sudden blurred vision on RE since 10 days ago. No history of red eye, eye pain, floaters, fotopsia, or trauma. Patient had history of hypertension that controlled with 5 mg amlodipine once daily. There is no history of diabetes. There is no information about smoking history. Patient had history of RE cataract surgery in Jakarta 5 years ago.

Patient's general examination was within normal limit. Ophthalmologic examination revealed the UCVA were 0. 32 on RE and 0.63 on LE. Ocular motility were full and IOP in normal limit. Both lens were cloudy. Other anterior segment examination were in normal limit. Funduscopic examination RE revealed submacular hemorrhage and drusen. Posterior segment of LE was within normal limit. OCT was taken, showed subretinal fluid on RE. Patient was diagnosed with AMD AREDS IV and pseudophakia RE.

Patient got total 5 injection of bevacizumab on his RE. The loading dose were on January 21st 2019, February 19th 2019 and March 19th 2019, with UCVA after 3rd dose was 0.8 (with patient's own spectacle correction). Patient got his 4th injection at April 25th 2019, and 5th injection at June 12th 2019 with final UCVA RE 1 week later were 0.8 (with patient's own spectacle correction). Patient then planned to continue her follow up at secondary health service.

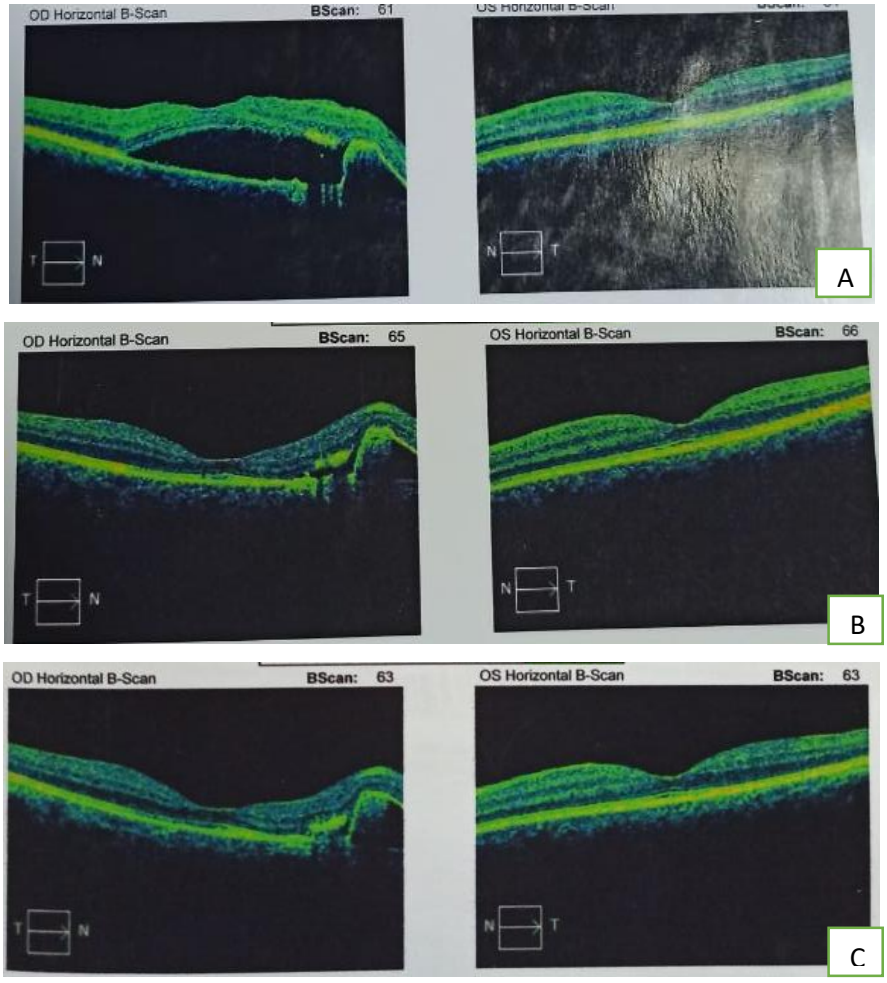

Figure 2.5. Patient's macular OCT A) January 17th 2019, B) March 26th 2019, C) June 19th 2019

III. Discussion

Age-related macular degeneration is the leading cause of blindness in the developed world in people over 50 years. In resource rich countries 10% people over the age of 65 and 25% over the age of 75 years have AMD. It is classified into

two main forms: non-neovascular (also known as “dry” or “nonexudative”) or neovascular (also known as “wet” or “exudative” or AMD AREDS IV). 80% patients with AMD are diagnosed with dry AMD, characterized by macular drusen, hyperpigmentation of RPE and atrophy. The remaining patients have AMD AREDS IV.[1,3,7]

AMD AREDS IV is responsible for the majority of AMD-associated vision loss and more acute in onset. Features of AMD AREDS IV is choroidal neovascular (CNV), manifesting as intraretinal, subretinal, or subretinal pigment epithelium serous fluid or hemorrhage, and end-stage fibrovascular disciform scar.[3,7,8] Macular optical coherence tomography (OCT) is important component for monitoring therapeutic respon and also as decision tools for next injection plan. In this case series, all five patients more than 60 years old and had AMD AREDS IV with various decreased of visual acuity as initial presentation when came to Cicendo National Eye Hospital. All patients have baseline OCT except patient from case two.

Population-based studies have demonstrated that of the risk factors for AMD, age is the first and foremost. Therefore as life expectancy improves with advances in medicine and public health the number of patients affected by AMD is also likely to increase. Additional risk factors include female sex, hypertension, hypercholesterolemia, cardiovascular disease, higher waist-to-hip ratio in men, positive family history, and cigarette smoking. On modifiable risk factors, cigarette smoking has been consistently demonstrated to be most significant.[1,3]

With increasing evidence that environment and health habits influence the development and progression of AMD, patients should be counseled to alter behaviors that put them at risk. Of particular importance are smoking cessation, obesity reduction, and blood pressure control. In this series, data about associated risk factors are lacking. All patients age was more than 60 years, consist of three female and two male patients. Three patients have hypertension, and one patient have both diabetic and hypertension. No data about smoking history in all patient.

Vascular endothelial growth factor is a key mediator of angiogenesis and has been isolated in CNV. Anti-vascular endothelial growth factor agents were better

than no anti-VEGF agents or other types of treatment for patients with AMD AREDS IV. There are three anti-VEGF agents that being used for AMD treatment; ranibizumab, bevacizumab and aflibercept.[2,8]

Tabel 2.1. The summary of five cases

The Summary of five Cases					
Age	69	60	69	61	62
Sex	Female	Female	Male	Female	Male
Comorbidity	Hypertension	Hypertension	No diabetic, No hypertension	Hypertension and diabetic	Hypertension
Number of injection	RE 5	LE 8	RE 6 LE 5	RE 6	RE 5
VA pre injection	RE 1/60 LE 0.08	RE 1.0 LE 0.05	RE 0.4 (CCKS) LE 0.2 (CCKS)	RE 0.16 LE 0.4	RE 0.32 LE 0.63
VA post injection	RE 0.4 LE 1/300	RE 0.63 LE 1/60	RE 0.25 LE 0.4 (CCKS)	RE 0.25 LE 0.4	RE 0.8 (CCKS) LE 0.63
Injection interval (month)	3-2-1-1	1-2-1-2-2-3-1	RE 1-1-1-2-8 LE 4-2-2-3	1-2-8-1-1	1-1-1-2

Two landmark phase 3 trials, Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) and Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR), demonstrated that ranibizumab gave large treatment benefits. Ranibizumab was administered by monthly intravitreal injection into the vitreous cavity. At 12 and 24 months, more than 90% of eyes treated with ranibizumab (0.5 mg) remained within 15 letters (three lines) of the presenting log MAR visual acuity chart compared to fewer than 64% of eyes treated with photodynamic therapy (ANCHOR), or 62% of eyes treated with sham injections (MARINA).[9]

Bevacizumab is 149-kDa full-length humanized immunoglobulin G1 kappa isotype antibody fragment that binds all isoforms of VEGF-A. Originally it was developed as a systemically administered chemotherapy. The use of bevacizumab

in the treatment of neovascular AMD has been off-label since its introduction in 2005.[8] In our hospital we use bevacizumab for intravitreal injection for AMD AREDS IV according to National Health Insurance service and restrictions.

The IVAN trial demonstrated that ranibizumab and bevacizumab had similar efficacy, and the frequency of serious adverse advents, such as arterial thrombotic events or hospital admission for heart failure, did not differ between the two drugs. the intravitreal dose of bevacizumab is 200-400 times lower than the intravenous dose. The CATT study found that ranibizumab and bevacizumab had similar efficacy on visual acuity and that the rates of death, myocardial infarction, and stroke did not differ. The disadvantages of intravitreal bevacizumab are the need to obtain the drug from compounding pharmacies and theoretical safety concerns due to the longer systemic half-life.[2,3,6,10,11]

Ocular adverse events after intravitreal injection of anti-VEGF agents, including endophthalmitis, retinal detachment, and IOP are rare across all studies. The rate of endophthalmitis in the CATT study was 0.06% (1 in 1700 injections). There is no greater risk associated with bevacizumab, suggesting that proper aseptic techniques can make bevacizumab as safe as drugs originally packaged for intravitreal injection. Short-term IOP increases within the first 30 minutes after injection usually resolve spontaneously, and intervention such as anterior chamber tap is rarely needed.[5,8] In this five cases, all patients did not have complaints or findings associated with ocular adverse events but there is no data about systemic adverse events.

The Comparison of AMD Treatments Trials (CATT study) compare bevacizumab and ranibizumab for neovascular AMD. Monthly bevacizumab and monthly ranibizumab had similar efficacies, and the results in the as-needed arms were also comparable. Similar results of VA to those seen in the ANCHOR and MARINA trials can be achieved without continuous dosing. The Prospective Optical Coherence Tomography (OCT) Imaging of Patients with Neovascular Age-Related Macular Degeneration (AMD) Treated with intraOcular Ranibizumab (PrONTO) trial showed that a reduction in treatment frequency can be achieved through rigorous tailoring of treatment to morphological parameters, with

comparable visual acuity outcomes. On the as-needed regimen, regular treatment is administered until the macula appears dry clinically and on OCT; after that treatment is only resumed when signs of recurrent exudation appear. The treat- and-extend regimen also involves administration of regular monthly treatment until the macula is dry; after that treatment continues at progressively increasing intervals. This more cautious second approach continues to treat inactive CNV (albeit at longer intervals between injections) to avoid sudden recurrence of exudation. As needed and treat and extend dosing had advantage for less frequent exposure to the local complications related to injection process.[1,3,9]

In this study all patients was planned for three consecutive monthly loading dose but only two patients got three loading dose with monthly interval (case three and five). Case five had with good VA improvement but in case two VA was decline. Most of the case's regiment did not have pattern as patient controlled not in that's regular as as needed or treat and extend protocol. In this group case one result in improvement of VA althougth the anatomical OCT evaluation show SMHRM; case two ended with conservative management, and case four had some VA improvement. Our hospital is tertiary health service so patients come from all over the country, at least all over the province. There was a period when bevacizumab not available. Although the injection covered by national health insurance, patient need to pay for accommodation and transportation. Patient with AMD also come from advance age so they are dependend for another family member to accompany them to hospital visit. Some of patients did not know that they need three loading dose monthly and then possibly continue based on their OCT on follow up visit. Data about risk factor also lacking, as no any data about evaluation, education and control of most modifiable risk factor. Suprisingly four of five patients had improvement in final VA. Longer stable intravitreal dosages of bevacizumab theoretically lead to better results with more longer injection interval. The existing data support the hypothesis that bevacizumab had longer half life than ranibizumab.[9]

Anti-VEGF pharmacotherapy delivered earlier in the course of neovascular AMD favorably affects visual prognosis. But available evidence suggests that

continued close follow-up and treatments longer than 2 years are needed to minimize visual loss. Depending on the reaction to injection, Ying et al found that visual acuity response at week 12 is more predictive of 2-year vision outcomes than either several baseline characteristics or week 4 response.[8,12] As in case two, patient had same VA after three loading dose, and there is no improvement after eigth dose.

Despite the effectiveness of anti-VEGF, there is large variation in response across patients, and response fluctuates over time within a patient. Disappointment over reactivation of the disease, late visual loss, and the chronicity of AMD AREDS IV is not rare.[12,13] In this study most patients was lost to follow up, as the last visit was more than four months ago. In addition to other barriers mention before, education about the disease progression, treatment plan and long term therapy is important for optimal result.

Earlier treatment, risk factor assessment, control and modification is important in comprehensive management. Delayed in injection could lead to suboptimal gain in VA or a preventable loss in VA. For best disease activity monitoring, each visit can consist of UCVA, best corrected VA, funduscopy and spectral-domain OCT examination. In this serial author use conversion chart to conversion logMAR VA to Snellen for VA because some VA were in logMAR and some in Snellen. It is recommended to use same VA chart for each visit, preferably logMAR chart for detailed evaluation of VA changes.

III. Conclussion

Optimal management of AMD AREDS IV including evaluation and control of risk factors, early treatment, timely injection of anti-VEGF according to disease activity and continuing education to patient itself. Patient adherence and continuity of medication availability is important to achieve better VA. Off label intravitreal bevacizumab is efficient and safety option to reduce the financial burden over multiple injections.

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