ORIGINAL ARTICLE

BROLUCIZUMAB FOR WET-AGED RELATED MACULAR DEGENERATION PATIENTS : TOO GOOD TO BE TRUE

Tania Purbonegoro[1], M. Eko Prayogo[2,3], A. Nurini Agni[2,3], Tri Wahyu W. [2,3], Supanji[2,3], Firman S.W. [2,3], M.B Sasongko[2,3]

[1]Ophtalmology Resident Faculty of Medicine, Public Health, and Nursing, Gadjah Mada University
[2]Department of Ophthalmology, Faculty of Medicine, Public Health, and Nursing, Gadjah Mada University
[3]Dr. YAP Eye Hospital, Yogyakarta
E-mail : tania.purbonegoro@mail.ugm.ac.id

ABSTRACT

Introduction & Objective: *Brolucizumab is the newest anti-vascular endothelial growth factor (anti-VEGF) drug. It showed superior anatomic outcomes compared to other anti-VEGF and noniferiority best corrected visual acuity (BCVA) results for Wet-Aged Related Macular Degeneration (Wet-AMD) patients. In Yogyakarta, its been only used in few patients and we want to report the Effectiveness and safety of brolucizumab in Wet-AMD patients in Yogyakarta.*

Method: *In this retrospective study, all neovascular AMD (nAMD) Patients who underwent brolucizumab intravitreal injections between December 2021 and January 2023 at YAP Eye Hospital were studied. Patient's demographic data, before and after intravitreal brolucizumab injections (central subfield thickness, intraocular pressure and BCVA) were assessed.*

Result :*This study included 6 eyes of 6 patients (3 women) with a mean age of 69.5 years old. The mean follow-up period was 27 ± 10.1 weeks after the first injection of brolucizumab. Three patients were naïve nAMD patient, never got any intravitreal injections and three anti-VEGF experienced nAMD patients with ranibizumab or aflibercept injections prior to brolucizumab. Mean BCVA at baseline (before brolucizumab injection) was 0.12 decimal (6/48) and was 0.29 decimal (6/20) at the last follow-up. Five out of six patients visual acuity were improved,one patient had constant bcva. Four out of six patient central subfield thickness were reduced, none of the patient intraocular pressure increased over 21 mmhg. None of the patient reported any signs of inflammation, vasculitis, or any other ocular or systemic adverse effects.*

Conclusion :*This limited data demonstrated that brolucizumab was safe and effective in stabilizing BCVA for both of nAMD patients who had undergone previous treatment with other anti-VEGFs agents and naive. Future larger multicenter collaborative studies are warranted.*

Keyword: *anti-vascular endothelial growth factor therapy; brolucizumab, neovascular age-related macular degeneration*

INTRODUCTION

Age-related macular degeneration (AMD) is a leading cause of blindness. characterized by the presence of progressive, degenerative abnormalities in the central retina (macula) (1). The aetiology of AMD is still unknown, but there are some risk factors such as older age (above > 75 years old), cigarette smoking, genetic susceptibility, and cardiovascular desease (2).

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AMD is categorized into two types : non-neovascular (dry or non-exudative) AMD and neovascular (wet or exudative) AMD (nAMD). nAMD is less prevalent than non-neovascular AMD, however, it causes more acute and severe loss of central vision. Currently, the licensed treatment options in nAMD are anti-vascular endothelial growth factor (anti-VEGF) that inhibits angiogenesis and vascular permeability and the only management proven to increase visual acuity and arrest disease progression Unfortunately, there are some therapeutic limitations of anti-VEGF therapy, such as high costs, repeated intravitreal injections, and unimproved or worsening vision outcomes despite aggressive treatment. (3).

Brolucizumab is the newest anti-VEGF drug. lt was approved for the treatment of nAMD by the US-FDA on October 7, 2019, followed by the European Commission's approval for use in the European Union on February 13, 2020 (4). Based on HAWK and Harrier trial (phase III studies), Brolucizumab demonstrated superior anatomic results with greater fluid resolution and noninferior best-corrected visual acuity compared to aflibercept(5). But, real-world clinical data of consecutive patients who have undergone this therapy especially in Yogyakarta has not yet been reported. In Yogyakarta, its been only used in few patients and we want to report the clinical outcomes regarding Efficacy and safety of brolucizumab in nAMD patients in Yogyakarta population.

METHODS

This was a single center, retrospective descriptive study. Data was collected from nAMD patients who underwent brolucizumab intravitreal injections between December 2021 and January 2023 at YAP Eye Hospital were studied. A total of 6 patients were reviewed. BCVA assessment, central subfield thickness (CST), intraocular pressure, and slitlamp examination (inflammation monitoring) were analyzed at baseline and the last follow-up after brolucizumab injection. CST were evaluated via spectral domain OCT (SD-OCT) device (Zeiss, Germany) device. Intraocular pressure were analyzed with non-contact tonometer. A minimum of 4-weeks follow-up was required to be included in the study. Data analysis was carried out using the IBM Stata version 12.

Institutional Review Board approval was obtained at each participating center and the investigators adhered to the tenets of the Declaration of Helsinki.

RESULTS

This study included 6 eyes of 6 patients. Mean age was 69.5 ± 6.2 (range 59 – 76 years). The mean follow-up period was 27 ± 10.1 weeks after the first injection of brolucizumab. The

male and female proportion was 3:3. The mean of preinjection BCVA, CST, IOP were as follows: BCVA decimal 0.12 ± 0.09, CST 274.2 ± 88.6 um, IOP 17.2 ± 1.9 mmHg. The mean of preinjection BCVA, CRT, IOP were as follows: BCVA decimal 0.29 ± 0.21, CRT 268.8 ± 134.94 um, IOP 16.9 ± 1.9 mmHg. Table 1 shows Demographic data, the means of before and after brolucizumab injections parameters (BCVA, CRT, IOP parameters)

Three patients were naïve nAMD patient, never got any intravitreal injections and three anti-VEGF experienced nAMD patients with ranibizumab or aflibercept injections prior to brolucizumab.

As shown in Table 2, five out of six patients visual acuity were improved, one patient had constant BCVA. Four out of six patient central subfield thickness were reduced, one was constant and one was increased. Eventhough there was increased in CST, but this patient's bcva was improved. None of the patient intraocular pressure increased over 21 mmhg. None of the patient reported any signs of inflammation, vasculitis, or any other ocular or systemic adverse effects.

DISCUSSION

Age-related macular degeneration (AMD) is an acquired degeneration of retina, leading cause of vision loss in elderly. There are some factors play a role in the etiology of AMD, such as Multiple genetic factors, lipid metabolism, oxidative stress and aging. AMD leads to significant central visual impairment through a combination of non-neovascular (drusen and retinal pigment epithelium abnormalities), and neovascular derangement (choroidal neovascular membrane formation)(1). Neovascular AMD causes more acute and severe loss of central vision (3).

Table 1 Demographic data, the means of before and after brolucizumab injections parameters (BCVA, CRT, IOP parameters)

Demographic Data	
Male/female (n)	3/3
Age (y)	
Mean ± SD	69.5 ± 6.2
Range	59 - 76
Follow-up period (weeks)	27 ± 10.1
Means of prior brolucizumab intravitreal injection (BCVA, CRT, IOP) parameters	
BCVA (decimal)	0.12 ± 0.09
CST (um)	274.2 ± 88.6
IOP	17.1 ± 1.9
Means of after brolucizumab intravitreal injection (BCVA, CRT, IOP) parameters	
BCVA (decimal)	0.29 ± 0.21
CST (um)	268.8 ± 134.94
IOP	16.9 ± 1.9

BCVA: Best-corrected visual acuity, CST: central subfield thickness, IOP: intraocular pressure

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nAMD is characterized by exudation from abnormally growing blood vessels in the macula owing to the release of VEGF. It leads to progressive degeneration of the RPE and photoreceptors(6). The retinal fluid accumulation, and edema can be evaluated in OCT (5,7). Anti VEGF-A agents have proven to improve visual outcomes for nAMD patient by targeting CNV lesions and preserving vision. But, the need of repeated intravitreal injections, burden of numerous visit, unimproved or worsening vision outcomes despite aggressive treatment lead to treatment nonadherence (8).

Current licensed treatment anti-VEGF agents are ranibizumab, aflibercept, and pegaptanib. Brolucizumab is the newest anti-VEGF drug. lt was approved for the treatment of nAMD by the US-FDA on October 7, 2019, followed by the European Commission's approval for use in the European Union on February 13, 2020 (5,9). Based on HAWK and HARRIR trial (2 similarly designed phase 3 trials comparing brolucizuma with aflibercept to treat nAMD), Brolucizumab was noninferior to aflibercept in visual function, anatomic outcomes favored brolucizumab over aflibercept. Overall safety with brolucizumab was similar to aflibercept. In those studies, brolucizumab injections is every 12 weeks, and every 8 weeks for aflibercept. With a molecular weight of approximately 26 kDa, brolucizumab has a smaller molecular mass than either aflibercept or ranibizumab, and, due to brolucizumab's high solubility, it can be delivered at a higher concentration, potentially resulting in a longer-lasting effect (5).

Table2. Detailed each Patient BCVA, CST, IOL, Side Effect before and after brolucizumab injection

Parameter		Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Follow-up duration		32	26	19	11	28	36
BCVA (Decimal)	**Pre**	0.05 (3/60)	0.2 (6/30)	0.16 (6/36	0.25 (6/24)	0.06 (4/60)	0.003 (1/300)
	Post	0.15 (6/18)	0.33 (6/18)	0.33 (6/36	0.25 (6/24)	0.67 (6/9)	0.033 (2/60)
CST(um)	**Pre**	322	232	219	170	282	420
	Post	264	199	197	170	248	534
IOP (mmHg)	**Pre**	19	19	18	17	14	16
	Post	15	17	20	15	16	18
Extraocular/ intraocular inflammation	**Pre**	No	No	No	No	No	No
	Post	No	No	No	No	No	No
Systemic Adverse Effects		No	No	No	No	No	No
Injection status		Naive	Naive	Experienced	Experienced	Experienced	Naive

To the best of our knowledge, real-world clinical data of consecutive patients who have undergone this therapy in Indonesia especially in yogyakarta has not yet been reported. In Yogyakarta, its been only used in few patients. From this limited study, Five out of six patients visual acuity were improved, one patient had constant bcva. Four out of six patient central subfield thickness were reduced, none of the patient intraocular pressure increased over 21 mmhg. None of the patient reported any signs of inflammation, vasculitis, or any other ocular or systemic adverse effects. There result seems too good to be true, and we also found similar result in BREW Study(4). But, BREW Study's subjects only consist of experienced nAMD patient that already had other antiVEGF injections meanwhile in this study consist of 3 naïve patient and 3 experienced patient.

There are limitations to the study due to its small sample size, short follow-up, and absence of a control group. Studies with large sample size and long-term follow up with a control group will be important to better understand the anatomic and vision efficacy, durability benefits of brolucizumab and the safety issues.

CONCLUSION

This limited data demonstrated that brolucizumab was safe and effective in stabilizing BCVA for both of nAMD patients who had undergone previous treatment with other anti VEGFs agents and naive. Future larger studies are warranted.

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