ORIGINAL ARTICLE

Comparison of Visual Acuity and Central Macular Thickness in Neovascular Age-related Macular Degeneration Patients with Subretinal and Intraretinal Fluid Treated with Intravitreal Bevacizumab

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ABSTRACT

Purpose: To compare visual acuity (VA) and central macular thickness (CMT) outcome of loading dose intravitreal bevacizumab treatment between neovascular AMD patients with character of predominant subretinal and intraretinal fluid.
Methods: Prospective study of loading dose intravitreal bevacizumab treated age-related macular degeneration, of which has a baseline macular morphology of subretinal or intraretinal fluid. VA, CMT, and their changes were evaluated during and after loading dose was completed.
Results: Thirty eight eyes (38 patients, mean age 66,95 years) were enrolled. 20 eyes were in subretinal fluid (SRF group) and 18 intraretinal fluid (IRF) group. Mean VA at baseline eventually was significantly different where SRF group (56,41 letters) were better than IRF group (43,72 letters). No statistically significant difference of mean VA change or CMT change between group, however VA in SRF group remained higher and CMT in SRF group were lower than IRF group.
Conclusion: Neovascular AMD, with both SRF and IRF at baseline, benefits from loading dose intravitreal bevacizumab treatment although mean visual acuity and mean central retinal thickness are better in those with SRF.

Keywords : neovascular age-related macular degeneration, subretinal fluid, intraretinal fluid, intravetrial, bevacizumab

Age-related macular degeneration (AMD) is one of the macular structure disorder causing blindness in population above 50 years old in developed countries[1], and similar trend is now seen in developing countries, including Indonesia. After a long treatment method evolution, anti-VEGF has been admitted as gold standard therapy for its efficacy in reducing central macular thickness (CMT) and improving visual acuity (VA) in neovascular AMD patients.[2-5]

Various study on AMD neovascular showed tremendous outcome of significant CMT reduction with anti-VEGF treatment. However 14-20% of those study revealed VA decrease of >15 ETDRS letters, and 7.5% experienced no macular improvement after one year follow up.[2,6] This fact has trigger the question whether there is certain factor which could predict anatomical or visual prognosis of neovascular AMD treated with anti-VEGF.

The world prevalence of AMD is 8.7%, which has been a serious issue in eye health of 65-74 years old population in Europe, North America and Australia. [1, 7-9] In Indonesia, Nggie[10] in 2008 found AMD prevalence in East Jakarta was as big as 4.3%. Hospital-based survey in Cipto Mangunkusumo Hospital in 2014 found 92 AMD cases, of which 35 were dry and 57 were wet.[11]

Modern imaging technology today has been able to identify the different location of fluid from choroidal neovascularization, whether located intraretinally due to retinal angiomatous proliferation (RAP), or subretinally due to typical classic AMD neovascularization. Several post-hoc analytic study found that intraretinal and subretinal fluid resulted in different VA prognosis. Ritter[12] and Simader[13] implied that intraretinal cystic lesion was one negative predictor of anti-VEGF treatment. This invention added up the hypothesis of different fluid location resulted in different outcome with anti-VEGF treatment.

Ranibizumab has been the gold standard of anti VEGF therapy in neovascular AMD, however bevacizumab has been declared as essential AMD therapy by WHO for it has comparable efficacy and safety to ranibizumab. Vitreoretina group of Indonesian Ophthalmology Asso-ciation and Cipto Mangunkusumo hospital as referral center in Indonesia have also recommended the usage of bevacizumab as standard therapy of neovascular AMD. As much as 29,92% bevacizumab administration in Cipto Mangunkusumo hospital was as neovascular AMD therapy with significant result.[14]

MATERIALS AND METHODS

This is a prospective clinical pre-post intervention study of two different group. Thirty eight eyes diagnosed with neovascular AMD were consecutively recruited from vitreoretina clinic in Cipto Mangunkusumo hospital, Jakarta. All patients were diagnosed both clinically and by OCT imaging, and were planned to undergo anti-VEGF bevacizumab intravitreal treatment.

Inclusion criteria are patients age patients age >50 years old, diagnosed with neovascular AMD and required anti-VEGF treatment, initial OCT imaging revealed either SRF or IRF or both due to AMD, naïve or recurrent AMD with last anti-VEGF therapy at least 8 weeks prior, VA range 31 – 75 ETDRS letters. While patients with other macular disorder, AMD with vitreomacular traction or vitreous hemorrhage or disciform scar, history of other treatment of retina (laser photcoagulation, photodynamic therapy, intravitreal corticosteroid injection, other surgeries), and other refractive media opacity which may interfere the result of this study were excluded.

All subjects underwent complete ophthalmological examination, including best corrected VA assessment with ETDRS chart, and OCT examination (CIRRUS HD-

Rerata BCVA (jumlah huruf)

OCT 5000) before injection, 4 weeks after 1st, 2nd, and 3rd injection of intravitreal bevacizumab. Injection procedure were performed based on standard operational procedure of CM hospital in operating theatre, and every patients also examined for early complication on clinic visit one day after injection.

Statistical analysis were performed using statistical package for the social sciences software (SPSS) version 20.0. Statistical differences between group were analysed using the independent T-test. P Value less than 0.05 is considered significant.

Table 1. Clinical characteristic of subjects

Characteristic	SRF N=20	IRF N=18	p
BCVA (letters), mean (SD)	56,41 (11,38)	43,72 (11,65)	**0,003**
CMT (μm), mean (SD)	316,89 (89,11)	377,56 (143,13)	0,129
IOP (mmHg), mean (SD)	11,61 (3,25)	13,01 (3,56)	0,262
PED, N			
- Yes	11(55,00%)	11(61,10%)	0,707
- No	9 (45,00%)	7 (38,90%)	
IS/OS junction disruption, N			
- Yes	6 (30,00%)	11(64,70%)	**0,037**
- No	14(70,00%)	6 (35,30%)	
SRHM, N			
- Yes	6(30,00%)	12(66,70%)	**0,026**
- No	14(70,00%)	6 (33,30%)	

RESULT

A total of 38 eyes of 38 patients were identified with subretinal fluid (SRF) and/or intraretinal fluid (IRF), and then classified into SRF group (20 eyes) or IRF group (18 eyes) based on the more dominant location. Of 38 eyes, 3 dropped out and only 35 eyes had complete set of data both VA and CMT after three times injection.

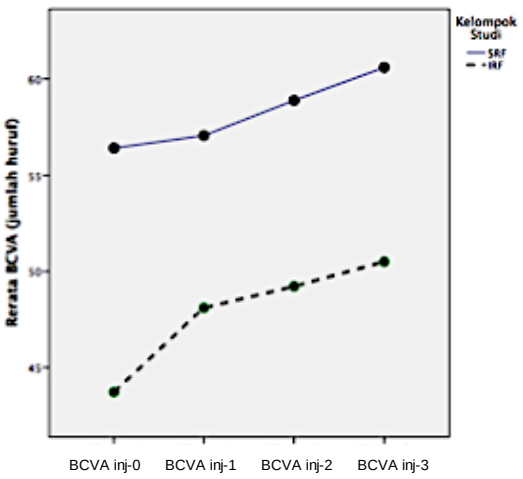

Fig 1. Mean VA during *loading dose*

The mean age was 66,95 years (standard deviation 7.77). There were 63.16% male and 36.84% female patients. The baseline VA in SRF group was significantly better (56.41 ETDRS letters) than in IRF group (43.72 ETDRS letter) with p value of 0.003. No significant difference of CMT between group at baseline. IS/OS junction disruption and subretinal hyperreflectivity material (SRHM) significantly present more in IRF group (64.70% and 66.7% respectively). (Table 1)

At the end of loading dose injection, VA of SRF group remained significantly better than IRF group (p=0.037). (Figure 1) Although IRF group showed bigger proportion of higher mean VA change, it was not statistically significant. (Table 2, Figure 2).

Subanalysis of other macular morphology showed that presence of SRHM in both group was significantly related to lower VA (Table 3). Neither IS/OS junction disruption nor presence of PED had any similar implication in this study.

Table 2. Mean VA change during loading dose

mean ΔBCVA (SD), (ETDRS letters)	group		p
	SRF (N=17)	IRF (N=18)	
ΔBCVA inj-1	0,65 (6,66)	4,39 (8,00)	0,144
ΔBCVA inj-2	0,65 (6,66)	5,50 (8,57)	0,312
ΔBCVA inj-3	4,18 (9,24)	6,78 (8,42)	0,390

information :
ΔBCVA inj-1 = number of readable letters change before injection on follow-up 4 weeks post 1st injection
ΔBCVA inj-2 = number of readable letters change before injection on follow-up 4 weeks post 2nd injection
ΔBCVA inj-3 = number of readable letters change before injection on follow-up 4 weeks post 3rd injection
p = p value of mean BCVA change between study group, independent T

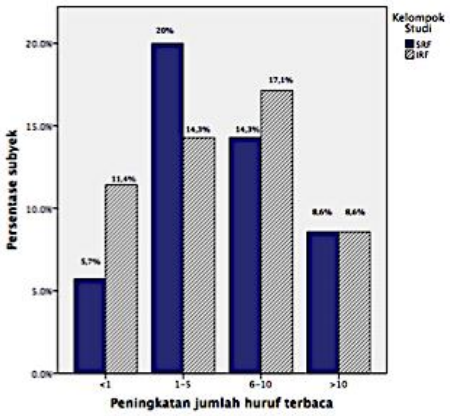

Fig 2. Distribution of mean BCVA change after loading dose (p=0,405)

Table 3. Mean VA after loading dose in relation with subretinal hyperreflectivity material (SRHM) characteristic

	mean BCVA (SD), (ETDRS letters)		p*
	SRF	IRF	
SRHM+ (N=18)	51,00(10,10)	45,83(11,79)	0,407
SRHM- (N=20)	64,58(12,49)	59,83(15,22)	0,489
p**	0,049	0,013	

information :
p* = p value of CMT between groups at the same follow up period, independent T-test
p** = p value of injection and study group correlation to CMT after loading dose, independent T-test

CMT was significantly lower in SRF group after 2nd and 3rd injection (p value 0.05 and 0.004 respectively). (Figure 3). Throughout loading dose, SRF group indeed showed bigger mean CMT difference, however this was not statistically significant. (Table 4).

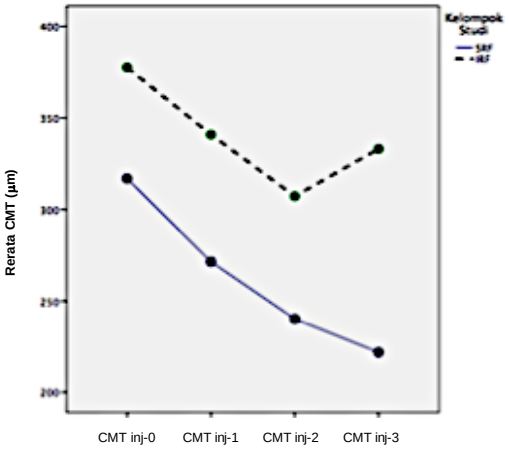

Fig 3. Mean CMT during loading dose

Table 4. Mean CMT change during loading dose

mean ΔCMT (SD), (µm)	group		p
	SRF (N=17)	IRF (N=18)	
ΔCMT inj-1	-56,32 (63,45)	-36,61 (80,76)	0,413
ΔCMT inj-2	-76,74 (76,26)	-70,28 (85,75)	0,810
ΔCMT inj-3	-95,05 (75,35)	-44,44 (123,99)	0,140

information :
ΔCMTinj-1 = mean CMT change on follow-up 4 weeks post 1st injection
ΔCMT inj-2 = mean CMT change on follow-up 4 weeks post 2nd injection
ΔCMT inj-3 = mean CMT change on follow-up 4 weeks post 3rd injection
p = p value of mean CMT change between study group, independent T test

DISCUSSION

Neovascular age-related macular degeneration (AMD) may present with various anatomic characteristic, depending on the involving macular structure. Optical Coherence Tomography (OCT) imaging technology has made it possible to identify those specific morphology of macula, including the presence and location of fluid related to neovascular AMD. Based on the involved structure, these fluid originally location in subretinal space (subretinal fluid) or intraretinally (intraretinal fluid). Neovascular AMD may present with any or

both of these fluid, with or without conjunction of other morphology such as IS/OS junction disruption, external limiting membrane disruption, subretinal hyperreflectivity material, pigment epithelial detachment (PED), or any others.

Identification of SRF and/or IRF become important in the treatment of neovascular AMD as guideline of anti-VEGF administra-tion. This prospective study tried to add the value of SRF/IRF iden-tification into the prognosis value of anti-VEGF treatment, bevacizumab in particular, by comparing the visual acuity and central macular thickness outcome between both group.

Demographic characters in this study were comparably distributed between groups. Although not statistically significant, proportion of male subjects were bigger (63.16%) than female (36.84%). However, there has been no study that can explain the relation of gender to AMD risk.[7] The mean age in this study was 66.95 (standard deviation 7.77) years old, and similar in both group. This group age is younger than in most AMD study in developed country, which was above 70 years.

Baseline VA was significantly better in SRF group, possibly due to the less severe photoreceptors disorganization compared to the process in IRF accumulation. Similar findings were claimed in CATT subanalysis study by Gianniou et al.[15] This different baseline VA was inevitable due to consecutive sampling and inability to perform randomization.

Within both study group there were VA improvement after every injection, and statistically significant after 2nd and 3rd injection. However no significance of mean VA change between group, similar to Gianniou et al[15] which performed follow up until month-36. Numerous study concluded IRF as a worse VA predictor after anti-VEGF injection, of which residual IRF was correlated with lower mean VA in every follow up. IRF also significantly associated with bigger risk of atrophy (OR 3.34) or fibrosis (OR 3.30), compared to SRF.[13, 15, 16] On the other hand, presence of SRF before anti-VEGF treatment revealed protector effect where the VA outcome was better than those without SRF.[17]

Distribution of VA change proportion at the end of loading dose was not significant between groups (p=0.836), but there was trend of bigger VA increase in IRF group. Nonetheless, mean VA of IRF group remained lower than SRF group. Several studies concluded better initial VA is a good prognostic factor of final VA.[18-20]

Gianniou et al[15] also found no significant difference of proportion with VA change $\geq$15 or $\leq$15 letters between IRF and SRF group after 12 months follow up. Ritter et al[12] mentioned IRF as the strongest negative predictive value in functional improvement. On the other hand, SRF was found to have protector effect in the 2nd year CATT subanalysis study[21]

In this study, subretinal hyper-reflectivity material (SHRM) signi-ficantly existed in both groups with lower VA. Willoughby in his study also found that AMD with SHRM presented with worse VA, especially when SHRM persisted and involved fovea. SHRM was presumed to interfere nutrition and metabolite exchange between RPE and photoreceptors.

Simader[13] in EXCITE study and Ritter[12] in MONTBLANC study found that IRF group experienced most significant resolution in loading dose period, but then recurrence rate increased in maintenance period. Meanwhile SRF group had less recurrence rate. Neurosensory obli-teration in IRF remained permanent despite its resolution.

Both study group showed significant CMT reduction, also significant difference between group. In 2nd and 3rd follow up, CMT in SRF group significantly thinner. However CMT change between groups was not significant. This showed that both group gained CMT resolution from intravitreal bevacizumab therapy.

Ma[22] in his study showed that bevacizumab effectively reduce CMT especially after first injection. Shin[6] found that subjects in IRF group were more likely to be refractory to bevacizumab. He tried to explain this by referring to bevacizumab's bigger molecule size that only effectively reached subretinal space, and its active transport was supported by Muller cells. Therefore in IRF group, where Muller cells were more disrupted, anatomical response to bevacizumab became inadequate.

CONCLUSION

This study showed that neovascular AMD, with both SRF and IRF at baseline, benefits from loading dose intravitreal bevacizumab treatment although mean visual acuity and mean central retinal thickness outcome are better in those with SRF. Further study with longer period of follow up is suggested to evaluate beyond loading dose phase.

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