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REAL-WORLD EVALUATION OF THE EFFECTIVENESS OF INTRAVITREAL BEVACIZUMAB INJECTION FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION AT CIPTO MANGUNKUSUMO NATIONAL REFERRAL HOSPITAL

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Abstract

***Introduction*:** *Neovascular age-related macular degeneration (nAMD) is a leading cause of visual impairment globally. While intravitreal anti-VEGF therapy is the standard treatment, real-world data on bevacizumab (IVB), the most accessible agent in Indonesian public hospitals despite being off-label, remains limited. This study aims to evaluate the effectiveness of IVB in patients with nAMD at a tertiary referral center in Indonesia.*

***Methods**: This retrospective study included patients diagnosed with nAMD who received IVB injections at Cipto Mangunkusumo National Referral Hospital between January and December 2017. Inclusion criteria encompassed patients with confirmed nAMD and available clinical data pre- and post-injection. Data on demographics, best-corrected visual acuity (BCVA), central macular thickness (CMT) measured by OCT, and IVB injection regimen were extracted from electronic medical records. Statistical analysis was performed using Wilcoxon signed-rank and Mann–Whitney U tests, with $p < 0.05$ considered statistically significant.*

***Result**: A total of 138 eyes from 131 patients (mean age: 66.7 years; 51% male) were analyzed. The median number of injections was three (range: 1–6). Mean BCVA showed a non-significant improvement from 1.19 to 1.14 logMAR (mean change: 0.05 logMAR; $p = 0.770$). Subgroup analysis indicated significant improvement in eyes with baseline VA worse than 1.32 logMAR (mean gain: 0.54 logMAR; $p < 0.01$) and a significant decline in eyes with baseline VA between 0.48 and 1.00 logMAR (mean loss: 0.21 logMAR; $p = 0.02$). CMT significantly decreased by an average of 108.33 µm ($p < 0.01$).*

***Conclusion**: IVB treatment for nAMD resulted in significant anatomical improvement and was particularly effective in patients with poor baseline visual acuity. These findings highlight the role of IVB in real-world clinical practice within resource-limited settings.*

Keywords: Neovascular age-related macular degeneration, anti-VEGF, intravitreal bevacizumab, visual acuity, central macular thickness **Cite This Article:** ADRIONO, Gitalisa Andayani et al. Real-World Evaluation of the Effectiveness of Intravitreal Bevacizumab Injection for Neovascular Age-Related Macular Degeneration at Cipto Mangunkusumo National Referral Hospital. **International Journal of Retina**, [S.l.], v. 8, n. 2, p. 165, oct. 2025. ISSN 2614-8536. Available at: <https://www.ijretina.com/index.php/ijretina/article/view/319>. Date accessed: 01 oct. 2025. doi: https://doi.org/10.35479/ijretina.2025.vol008.iss002.319...

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INTRODUCTION

Age related macular degeneration (AMD) is a leading cause of visual impairment worldwide, with a global prevalence of 200 million.[1] The prevalence of AMD in Asian countries is generally around 3% – 19.5%.[2] AMD can be classified into atrophic AMD (dry or non-exudative AMD) and neovascular AMD (wet AMD).[3,4] In neovascular AMD (nAMD), macular damage and choroidal neovascularization (CNV) play a huge role in impairing visual acuity.[5] Several factors contribute to the development of neovascularization, one of those is vascular endothelial growth factor (VEGF), thus making anti-VEGF as the main treatment of choice for nAMD cases.[4]

Several studies have evaluated the therapeutical effect of anti-VEGF in nAMD, dating to the MARINA and ANCHOR trials where intravitreal anti-VEGF was injected monthly for 24 months and demonstrated the superiority of anti-VEGF therapy.[6] The PrONTO study introduced a more flexible regimen, utilizing an initial loading dose of anti-VEGF for the first three months, followed by a pro re nata (PRN) approach.[7] Later, subsequent study advocated for the 3-month loading dose followed by a treat-and-extend (TAE) method.[8]

Despite these findings, real-world studies from Europe revealed variability in the implementation of these protocols, with many clinical settings deviating from recommended guidelines.[9] In Indonesia, the first formal guideline for intravitreal anti-VEGF injections including bevacizumab (AVASTIN ®) use was introduced in 2012, but adherence was found to be inconsistent among practitioners. Economic burden in long-term anti-VEGF treatment approach and extensive supporting examinations, patient's impaired mobility, and mandatory long-term follow up are several determinants which greatly impact the outcomes from anti-VEGF therapy in nAMD patients.[10–13] With all these factors influencing efficacy, this study aims to evaluate the treatment patterns and therapeutic outcomes of bevacizumab, the most widely available intravitreal anti-VEGF therapy for nAMD patients at a tertiary referral hospital in Indonesia.

METHOD

All nAMD patients who were diagnosed based on clinical examination and macular optical coherence tomography (OCT), and who received intravitreal anti-VEGF bevacizumab injection at the Vitreoretinal Division in Cipto Mangunkusumo National General Hospital from January to December 2017, were included in this retrospective cohort study. Clinical examinations and OCT assessments were conducted by ophthalmology residents under the supervision of attending vitreoretinal consultants.

Medical records served as the data source for this study. Records were reviewed by one ophthalmology resident to collect demographic and clinical information, including age, gender, laterality of the affected eye, best-corrected visual acuity (BCVA), and central macular thickness (CMT) measured by OCT. Data were then extracted by fellow authors. Visual acuity values were converted from the Snellen scale to logarithm of the minimum angle of resolution (logMAR). The number of injections administered, whether the loading dose was completed, and the follow-up interval after the last injection were also recorded. Patients were excluded if they had incomplete medical records, lacked post-injection examinations, or had received intravitreal agents other than bevacizumab during the study period. Data extraction was performed by one author and subsequently validated by the other authors to ensure accuracy.

The bevacizumab injection protocol consisted of a loading dose of three monthly injections, followed by a pro re nata (PRN) regimen. Reinjection under the PRN protocol was determined by the attending vitreoretinal consultant based on evidence of disease activity.

Statistical analysis was conducted using SPSS version 24.0 (IBM Corp., USA) for MacOS. Quantitative variables are presented as median (range) or mean (standard deviation), depending on the normality of the data, while qualitative variables are expressed as proportions. Independent comparisons of categorical data were performed using the Mann–Whitney U and Fisher's exact tests. The Wilcoxon signed-rank test was used for paired sample comparisons. A p-value of <0.05 was considered statistically significant.

RESULTS

Our study identified 148 patients who met the inclusion criteria; however, 17 were excluded due to incomplete medical records. A total of 138 eyes from 131 patients were included in the analysis. The mean age of participants was 66.7 years (SD ± 7.9 years), with 94% presenting with unilateral nAMD. The gender distribution was nearly equal, with 51% male and 49% female. The mean BCVA prior to injection was 1.19 logMAR (SD ± 0.78), with the majority of participants (39.1%) having an initial BCVA between 0.48 and 1.00 logMAR. The mean central macular thickness (CMT) before injection was 382.95 µm (SD ± 155 µm), and the average follow-up duration was 14 months (SD ± 3 months).

The bevacizumab injection protocol that was adapted in this study at the time was a loading dose administered three times, followed by a PRN injection. The median for number of intravitreal bevacizumab injections for our patients within the one-year study period was three injections, ranging from one to six injections. Other demographic and clinical findings of our subjects are listed in **Table 1**.

Tabel 1. Demographic and Clinical Data Before Injection (n = 131)

Age (years)	66.7 (SD ± 7.9)	
Gender	Male	67 (51.0%)
	Female	64 (49.0%)
Affected eye	Unilateral	124 (94%)
	Bilateral	7 (6%)
Average BCVA (logMAR (Snellen *equivalent*))	1.19 (4/60) (SD ± 0.78)	
	0-0.48 (6/6 – 6/15)	27 (19.6%)
	>0.48 – 1.00 (<6/15 – 6/60)	54 (39.1%)
	>1.00 – 1.32 (<6/60 – 3/60)	11 (8.0%)
	>1.32 (<3/60)	46 (33.3%)
Average CMT	382.954 (SD $\pm$ 155)	
Average follow up period (months)	14 (SD $\pm$ 3)	
Number of injections during study period (median (minimal - maximum))	3 (1 – 6)	

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Pre- and post-injection BCVA data were only able to be collected from 93 subjects. The average BCVA before injection was 1.19 logMAR (4/60; SD ± 0.78) and after injection was 1.14 logMAR (5/60; SD ± 0.70). The mean BCVA change before and after injection was -0.05 (p = 0.770; 95% CI -0.13 – 0.17). Subjects were categorized into 4 categories according to their initial BCVA, and the >0.48 – 1.00 logMAR range was found to have a significant worsening of visual impairment after injection, reaching an average of 0.21 logMAR reduction in visual acuity (p = 0.02, 95% CI 0.04 -0.39). Concurrently, the group with the worst starting BCVA (>1.32 logMAR) demonstrated a significant 0.54 logMAR (p < 0.01; 95% CI -0.12 – 0.17) increase in BCVA post-injection. Changes in BCVA after bevacizumab injection can be observed in **Table 2**.

Tabel 2. Change in BCVA (logMAR)

BCVA pre-injection (logMAR)	Number of eyes	Average BCVA pre-injection (logMAR (Snellen))	Average BCVA post-injection (logMAR (Snellen))	Average BCVA change (logMAR)	P	95% CI
0 - 0.48	17	0.25 (6/7.5)	0.56 (6/12)	0.31	0.49	-0.40 – 0.03
>0.48 - 1.00	41	0.80 (6/45)	1.01 (6/60)	0.21	0.02	0.04 – 0.39
>1.00 - 1.32	6	1.30 (3/60)	1.27 (4/60)	0.25	0.88	-0.44 – 0.39
>1.32	29	2.17 (1/300)	1.62 (1/60)	-0.54	<0.01	-0.83 – -0.25

In this study, post-injection central macular thickness data was garnered from 115 subjects. In general, a significant reduction in central macular thickness was shown in this study, with a mean change of 108.33 µm (p < 0.01; 95% CI 75.5 – 141.2). A detailed analysis of each group suggested that the group with the best starting BCVA before injection (0 – 0.48 logMAR) exhibited the greatest improvement in central macular thickness (106.76 µm; p = 0.03; 95% CI 11.82 – 201.71). A significant change in central macular thickness was also observed in the worst initial BCVA group (182.50 µm; p < 0.01; 95% CI 109 – 254). Other data regarding the change in central macular thickness can be seen in **Table 3.**

Tabel 3. Change in central macular thickness

BCVA (logMAR)	Number of eyes	Average central macular thickness pre-injection	Average central macular thickness post-injection	Average central macular thickness change	P	95% CI
All eyes	115	394.97	286.64	108.33	<0.01	75.5 – 141.2
0 - 0.48	17	362.88	256.12	106.76	0.03	11.8 – 201.7
>0.48 - 1.00	50	351.92	299.76	52.10	<0.01	21.10 – 83.23
>1.00 - 1.32	8	344.00	250.87	93.12	0.043	4.12 – 182.12
>1.32	40	472.62	290.375	182.50	<0.01	109 – 254

Our study also did a subgroup analysis on the change of BCVA while grouping our subjects based on their therapy regimen, complete or incomplete loading dose. Sixty-five subjects were a part of the complete loading dose group, while 28 subjects were categorized into the incomplete loading dose group. Our study suggested a statistically significant BCVA improvement within the complete loading dose group (-0.05 logMAR; p = 0.03; 95% CI -0.186 – -0.03), whereas the incomplete loading dose group underwent worsening of visual acuity, though the result was not statistically significant (p = 0.54; 95% CI -0.19 – -0.36). **Table 4** depicts the association between intravitreal bevacizumab dose on patient's visual outcome.

Tabel 4. Change in BCVA (logMAR), grouped by injection dose

	Number of eyes	Average change in BCVA (logMAR)	P	95% CI
Complete loading dose	65	-0.05	0.03	-0.186 – -0.03
Incomplete loading dose	28	0.08	0.54	-0.19 – 0.36

Seventy-seven subjects were followed up equal to or more than 6 months, and 16 subjects were followed up no later than 6 months. Subjects in both groups experienced changes in visual acuity. The group with a follow up period of equal to or more than 6 months experienced improved visual acuity, while those who underwent an average follow up period of less than 6 months experienced worsening visual acuity. However, changes in visual acuity in both groups did not reach statistical significance (**Table 5**).

Tabel 5. Change in BCVA (logMAR), grouped by mean follow up duration after last intervention

	Number of eyes	Average change in BCVA (logMAR)	P	95% CI
Equal to or more than 6 months	77	-0.04	0.61	-0.20 - 1.21
Less than 6 months	16	0.33	0.08	-0.05 - 0.70

DISCUSSION

This study evaluated the real-world effectiveness of intravitreal bevacizumab (IVB) for neovascular age-related macular degeneration (nAMD) in a tertiary hospital setting in Indonesia. Among 138 treated eyes, the overall mean best-corrected visual acuity (BCVA) improved from 1.19 logMAR to 1.14 logMAR; however, this change was not statistically significant (mean difference: 0.05 logMAR; p = 0.770). In contrast, central macular thickness (CMT) showed a significant mean reduction of 108.33 µm (p < 0.01), reflecting anatomical improvement in most patients. Subgroup analysis revealed that patients with baseline BCVA worse than 1.32 logMAR showed significant visual improvement (mean gain: 0.54 logMAR; p < 0.01), while those with baseline BCVA between 0.48 and 1.00 logMAR experienced significant deterioration (mean loss: 0.21 logMAR; p = 0.02)

Patients with nAMD at our tertiary eye center tend to receive anti-VEGF injections at a younger age

compared to those in other real-world study populations. In our cohort, the mean age was 66.7 years, whereas Providência et al. reported an average age of 79 years in their study population.[14] Similarly, studies by Rao et al. and Ciulla et al. found mean ages of 80 and 82 years, respectively.[11,15] Regarding gender distribution, male participants slightly predominated in our study (51%), comparable with the findings of Providência et al. (52% male and 48% female).[14] In contrast, Rao et al. and Ciulla et al. reported a higher proportion of female participants (63%).[11,15]

Numerous real-world studies, including ours, indicate that randomized controlled trials (RCTs) often report better therapeutic outcomes.[11–13,15,16] For example, the LUCAS, CATT, and IVAN trials demonstrated statistically significant results.[10,17,18] In contrast, real-world studies tend to yield less favorable outcomes, likely due to differences in patient populations. Real-world studies often include patients with more diverse and advanced disease stages that are typically excluded from RCTs. Additionally, RCTs have strict inclusion and exclusion criteria, while real-world studies aim to capture more representative data. Factors such as patient compliance and limited access to therapy, like bevacizumab intravitreal injections, may further contribute to these discrepancies.

We observed that monotherapy with bevacizumab led to visual acuity improvement in Indonesian nAMD patients after one year. Most patients in this study fell into the categories of moderate visual impairment (logMAR >0.48 – 1.00, equivalent to 6/18 – 6/60) and blindness (logMAR >1.32, equivalent to <3/60). The mean change in logMAR in our study was statistically insignificant, consistent with findings from a US-based real-world study of 13,859 medical records, which reported a statistically insignificant 0.053 logMAR increase in visual acuity following bevacizumab treatment.[15] These results contradict several published reports which revealed a significant result in visual acuity after anti-VEGF injection.[12,13,19]

Our data were mostly stratified according to the subject's baseline BCVA. Statistically significant decrease in visual acuity was found on subjects in the moderate visual impairment group (0.21 logMAR), while the severe visual impairment group showed a profound visual acuity correction to -0.54 logMAR. Ciulla et al. generated similar results, where subjects in the 6/12-or-more visual acuity group tend to face deterioration in visual acuity, up to 4.5 – 5.2 letters using the ETDRS chart. Conversely, those in the baseline BCVA 6/60-or-less group displayed visual improvement to 8.8 – 19.9 letters of the ETDRS chart.[11]

The contrasting results across baseline VA subgroups in our study may be partially attributed to differences in real-world treatment adherence, reinjection thresholds, and follow-up variability. Patients with better initial VA may exhibit subtler signs of disease activity, which can delay reinjection decisions under the PRN protocol. In contrast, those with severe baseline impairment are more likely to present with overt fluid or hemorrhage, necessitating prompt reintervention. These opposing trends may explain the lack of significant change in the overall cohort, as visual improvement in one subgroup was offset by deterioration in another.

Additionally, the data showed that patients with better baseline visual acuity tended to experience a decline at the end of follow-up. These individuals may be more sensitive to variability in injection frequency than those with worse initial vision. Notably, this decline may be irreversible even with intensified anti-VEGF treatment. Such outcomes are consistent with the "ceiling and floor" effect, wherein patients with relatively good baseline VA have

limited room for improvement, while those with poor VA are less likely to deteriorate further. [23] Nonetheless, both groups remain vulnerable to worsening without appropriate retreatment strategies, thus a more careful selection of therapy and injection regimen are required.

The average central macular thickness in patients in this study was 382.95 µm. However, we found our subjects' visual acuity before injection to be relatively worse compared to the data reported by other real-world studies.[11,15,16] Similarly, the average central macular thickness of our subjects before injection (382 µm) is lower than other studies, such as Garweg et al. (601 µm) and Park et al. (418 µm).[12,24] At the end of the follow-up period, changes in central macular thickness that were seen in our subjects after one year of bevacizumab injection, reaching a mean decrease of -108.33 µm relative to the baseline value. Several studies reported a mean reduction in central macular thickness as well. Garweg et al. documented a mean central macular thickness decrease of -127.4 µm after a year of three ranibizumab injections.[12] Park et al. evaluated CMT difference after a year of bevacizumab/ranibizumab/aflibercept injections and found an average decrease in CMT of -152.88 µm in the bevacizumab group.[24] These results are similar with the outcomes described by several large RCT studies, namely the LUCAS, IVAN, and CATT trials, where they reported a mean CMT reduction of -113 µm, -133.8 µm, and -162.07 µm respectively.[10,18,19]

Stratification of data in this study was also done based on the dosage of intravitreal injection they received, the complete and incomplete loading dose groups. We observed a significant improvement in BCVA for the complete loading dose group, whereas those with lower amount of bevacizumab injections had a generally lower degree of visual improvement. These results are consistent with several other real-world studies, strengthening the idea that the amount of anti-VEGF injection has an impact on the visual outcome of nAMD patients.[15,16,22]

And the average duration of follow-up was 14 months. In our study, statistical analysis of patients who underwent follow-up of equal to or more than 6 months and less than 6 months did not show any significant association with improvement in visual acuity. This is different from Ciulla et al., which suggested that a longer follow-up period showed better visual acuity results compared to patients who experienced a shorter follow-up period.[11] Gilles et al. also found the same result, namely that patients with shorter follow-up period tended to experience a greater decline in vision.[25]

Loss to follow-up is often associated with unsatisfactory results of anti-VEGF injection therapy, problems with transportation to the nearest healthcare facility, cost of therapy, senior age, fatigue from multiple therapy regimen, and/or death. In some studies, the reason for lost to follow up was poor baseline visual acuity at the start of therapy. Another reason is a change of disease state to inactive, which is proven via OCT. However, various studies have shown that follow-up after nAMD has become inactive remains important considering the possibility of recurrence and worsening visual prognosis.

The strengths of the study include its relatively large sample size and comprehensive analysis of both visual acuity and central macular thickness outcomes. However, limitations such as its retrospective design, lack of a control group, and reliance on medical record data, which may introduce selection bias and incomplete follow-up, should be noted. Additionally, the use of a PRN injection regimen may limit the generalizability of the results to populations receiving fixed or TAE protocols. Future studies should consider

prospective or multicenter approaches that explore alternative regimens such as treat-and-extend, with careful monitoring of retreatment intervals, baseline anatomic features, and real-world adherence factors that may affect long-term outcomes.

CONCLUSION

Our study demonstrates bevacizumab injection ability to refine the visual acuity of nAMD patients with an impaired vision. Cases with greater initial BCVA were seen to have a higher chance of acquiring worse visual impairment, thus a strict supervision especially during therapy period is necessary to prevent such complication. Moreover, the dosage of bevacizumab intravitreal injection had a paramount effect on visual outcome, hence complete anti-VEGF injection loading dose should be implemented to achieve maximal outcomes.

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