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Original Research

INTERLEUKIN-1 (α&B) POLYMORPHISM AND BEVACIZUMAB RESPONSE IN NEOVASCULAR AMD: JOGJA AGEING AND GENOMIC AMD DETERMINANT (JAGAD) STUDY NUMBER 4

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ABSTRACT

Introduction: Interleukin-1 (IL-1) gene polymorphisms may affect the response to anti–vascular endothelial growth factor (VEGF) therapy in neovascular age-related macular degeneration (nAMD) through their role in regulating inflammatory pathways. This study evaluated associations between IL-1 (α&β) and anatomical outcomes following intravitreal bevacizumab.

Methods: We carried out a multicenter retrospective study that included 84 eyes from 71 patients with nAMD across three tertiary referral hospitals in Yogyakarta, Indonesia. Patients were categorized as responders or non-responders according to whether a reduction of more than 10% in central macular thickness (CMT) was achieved one month after bevacizumab injection. Peripheral blood samples were collected for DNA extraction and genotyping.

Results: Responders demonstrated significantly greater CMT improvement despite having higher baseline values (389.0 μM) compared with non-responders (303.0 μM, P = 0.033). At one-month follow-up, responders achieved substantially lower CMT measurements (257.0 μM, P = 0.002). The IL-1α risk genotype was not detected in both groups. In addition, the genotype distribution for IL-1α showed no statistical significance difference across age, sex, best corrected visual acuity (BCVA), and CMT. Genetic analysis indicated that individuals carrying the IL-1β T allele had a 39% lower likelihood of being non-responders (OR 0.61; 95% CI 0.32–1.16). Moreover, the CT and TT genotypes showed stronger trends, with reductions in non-response risk of 34% (OR 0.66; 95% CI 0.15–2.88) and 67% (OR 0.33; 95% CI 0.06–1.72), respectively. However, these associations did not reach statistical significance.

Conclusion: Our findings indicate a potential protective effect of the IL-1β -511C/T polymorphism against poor response to bevacizumab therapy, though statistical significance was not achieved. Further investigation with larger sample sizes is necessary to confirm the predictive value of IL-1 genetic variations for anti-VEGF therapy outcomes in patients with nAMD.

Keywords: AMD, anti-VEGF, IL-1α, IL-1β, polymorphism

Introduction

Age-related macular degeneration (AMD) has been known as one of the main causes of irreversible visual impairment among individuals aged 50 years and older, affecting million cases in the world.[1] The global prevalence of AMD among people aged 45–85 years is estimated at 8.69%, lower in Asians than in Europeans (7.4% vs. 12.3%).[2] The exact prevalence of AMD in Indonesia is still unknown but estimated to be around 125,501 cases in 2019, doubled compared to 1999, with an age-standardized rate of 67.24%.[3] However, although the number of cases was increasing, the age-standardized was decreasing due to population aging. AMD not only causes clinical impact, but also economic and healthcare burden. The mean outpatient visit cost of patient with active choroidal neovascularization (CNV) in the United States was $8,658 [SD $11,612], four and seven times higher than patients with inactive CNV and inactive scar ($2,406 [SD $5,510] and $1,198 [SD $3,035], respectively).[4]

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Current first-line therapy for nAMD was intravitreal inhibition of vascular endothelial growth factor (VEGF) due to its efficacy in maintaining visual acuity.[5,6] However, treatment response varies considerably between patients, and repeated injections significantly increased the treatment cost.[4] The interleukin-1 (IL-1) family, with a particular focus on IL-1α and IL-1β, has emerged as a crucial mediator in nAMD pathogenesis through pro-inflammatory mechanisms that promote retinal pigment epithelium (RPE) damage and VEGF-driven neovascularization.[7,8] While these cytokines' inflammatory roles are well-established in nAMD progression, their genetic polymorphisms remain inadequately explored as potential modifiers of anti-VEGF treatment response. Previous genetic studies of IL-1 in ocular diseases have primarily focused on conditions like keratoconus,[9,10] leaving a significant knowledge gap regarding their role in nAMD treatment outcomes.

This study specifically investigates the relationship between single nucleotide polymorphisms within the IL-1α and IL-1β genes and anatomical treatment responses to intravitreal bevacizumab in patients with nAMD. By examining these genetic variations within the inflammatory pathway, our research aims to identify potential biomarkers that could enhance understanding of treatment response variability and contribute to more personalized therapeutic strategies for nAMD management.

Methods

Study Design and Patient Recruitment

This retrospective observational cohort study compared central macular thickness (CMT) before and one month after intravitreal bevacizumab injection between two groups: responders and non-responders. These groups were further stratified by three IL-1α −889C/T (rs1800587) and IL-1β -511C/T (rs16944) polymorphic genotypes: non-risk (CC genotype), heterozygous (CT genotype), and risk (TT genotype). Treatment response was defined as a reduction of more than 10% in CMT one month after injection compared with baseline. This threshold was established on the basis that an early 10% reduction in CMT is a clinically observed marker for a subsequent positive treatment course.

This study was conducted across three ophthalmology centers in Yogyakarta, Indonesia: (1) Dr. Sardjito General Hospital, (2) YAP Eye Hospital, and (3) Dr. S. Hardjolukito Air Force Central Hospital. Inclusion criteria required patients to be aged ≥50 years with a clinical diagnosis of nAMD confirmed by dilated fundus examination and macular optical coherence tomography (OCT) and no prior anti-VEGF therapy within the preceding six months. Exclusion criteria included previous retinal surgery; retinal diseases other than nAMD such as diabetic macular edema (DME) and central serous chorioretinopathy (CSCR); current or recent (within the past six months) systemic or topical corticosteroid or immunosuppressive therapy; acute or chronic inflammatory or autoimmune diseases; active infection; malignancy; and systemic conditions known to significantly affect inflammatory pathways or cytokine expression, including IL-1α and IL-1β polymorphisms. Potential confounding factors, including age, blood pressure profiles, body mass index (BMI), and smoking status, were recorded and accounted for in the analysis.

Patients Assessment

The eligible patients underwent comprehensive baseline and follow-up evaluations. The ophthalmologic examinations included: (1) best-corrected visual acuity (BCVA) testing using a Snellen chart, (2) intraocular pressure (IOP) measurement via non-contact tonometry, (3) anterior segment and fundus evaluation using slit-lamp biomicroscopy with 78D lens indirect ophthalmoscopy, and (4) CMT measurement by Spectral Domain OCT (Zeiss Cirrus OCT). All examinations were performed under pupil dilation following topical mydriatic administration. A vitreoretinal consultant confirmed all AMD diagnoses.

Genetic Analysis and Treatment Protocol

Peripheral blood samples were collected for DNA extraction using QIAamp DNA kits prior to the injection. Participants received intravitreal bevacizumab (Avastin®) injections administered by a single vitreoretinal specialist (SPJ), followed by a 5-day prophylactic course of topical Optiflox®. At the 1-month follow-up, we repeated BCVA testing, IOP measurement, anterior segment examination, and CMT evaluation while monitoring for adverse events. Treatment response was defined as a reduction of more than 10% in CMT relative to baseline.

Genotyping for the IL-1α -889C/T and IL-1β -511C/T polymorphism was conducted using restriction fragment length polymorphism polymerase chain reaction (RFLP–PCR). The reaction employed the following primers: (1) IL-1α -889C/T: forward 5'-GCATGCCATCACACCTAGTT-3' and reverse 5'-TTACATATGAGCCTTCCATG-3'; (2) IL-1β -511C/T: forward 5'-CTCTAACTCTTTATATAGGAA-3' and reverse 5'-GATTGATTTTATCAACAGGCA-3'.

Each 20 µL PCR reaction contained: 10 µL Bioline PCR mix (Bioline, Meridian Bioscience, Ohio, USA), 1 µL each of forward and reverse primer, 7 µL nuclease-free water, and 1 µL DNA template (~50 ng). Amplification was conducted in a Veriti™ 96-Well Fast Thermal Cycler under the following conditions: initial denaturation at 95°C for 10 minutes; 35 cycles of denaturation (95°C, 45 seconds), annealing (58°C, 45 seconds), and extension (72°C, 45 seconds); final extension at 72°C for 5 minutes; followed by indefinite hold at 15°C.

For RFLP analysis, 15 µL PCR product was digested overnight at 37°C in a 25 µL reaction mixture containing 0.5 µL enzyme (NcoI/IL-1α and EcoRI/IL-1β), 2.5 µL buffer, and 7 µL nuclease-free water. Digested products were resolved by 3% agarose gel electrophoresis (40 minutes) and visualized under UV light. The interpretation is was as follows: 1) IL-1α: CC had two bands of 174bp and 19 bp; CT had three bands of 174bp, 19bp, and 193bp; and TT had one band of 193bp; 2) IL-1β: CC had one band of 203bp; CT had three bands of 203bp, 184bp, and 19bp; and TT had two bands of 184bp and 19bp.

Statistical Analysis

Data were analysed using STATA v17. As for the cohort component, changes in CMT pre- and post-bevacizumab injection within genotype groups (C/C vs. C/T+T/T) were analyzed using paired t-tests (normal data) or Wilcoxon signed-rank tests.

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Differences in CMT response were assessed using independent t-tests or Mann-Whitney U tests, as appropriate. The association between genotype and treatment response was evaluated using logistic regression analysis.

Result

In this study, we included 84 eyes from 71 patients diagnosed with nAMD who received bevacizumab injections. Table 1 presents the demographic and clinical characteristics of the 39 responders and 43 non-responders. The responder group was significantly older than the non-responder group (median 70.0, IQR 65.0–77.0 years vs 64.5, IQR 61.0-69.0 years; P = 0.007). Similarly, responders demonstrated significantly lower diastolic blood pressure (median 80.0, IQR 71.0–87.0 mmHg vs 85.0, IQR 75.0–92.0 mmHg; P = 0.036). No significant differences were found between the groups in terms of sex distribution, systolic blood pressure, BMI, or smoking status (all P > 0.05).

Table 1. Baseline characteristics of the participants

	Responder N = 39	Non-responder N = 43	*P*
Age	70.0 (65.0–77.00)	64.5 (61.0–69.0)	0.007[1]
Sex			0.82[2]
Male	13 (33%)	15 (36%)	
Female	26 (67%)	27 (64%)	
Systolic blood pressure	145.0 (130.0–161.0)	147.0 (136.0–161.0)	0.69[1]
Diastolic blood pressure	80.0 (71.0–87.0)	85.0 (75.0–92.0)	0.036[1]
Body mass index	24.4 (22.1–25.7)	24.1 (21.6–27.1)	0.79[1]
Smoking			0.58[2]
No	21 (55%)	24 (62%)	
Yes	17 (45%)	15 (38%)	

Data are presented as the median (IQR) for continuous measures, and n (%) for categorical measures.
[1] Wilcoxon rank-sum test
[2] Chi-square test

Clinical characteristics at baseline and one month post-injection are summarised in Table 2. Responders demonstrated poorer median BCVA than non-responders both at baseline (1.3 vs. 1.1 logMAR) and post-injection (1.2 vs. 1.0 logMAR); however, these differences did not reach statistical significance (P = 0.27 and P = 0.097, respectively). Responders exhibited a significantly higher median CMT at baseline (389.0 vs. 303.0 µM, P = 0.033). After one month, this relationship reversed, with responders achieving a significantly lower median CMT (257.0 vs. 335.0 µM, P = 0.002), indicating a positive therapeutic response.

Table 2. Clinical characteristics at baseline and post-anti-VEGF treatment for nonresponders and good responders

	Responder N = 39	Non-responder N = 43	*P*
BCVA baseline (logMAR)	1.3 (0.9–1.8)	1.1 (0.7–1.5)	0.27
BCVA post-injection (logMAR)	1.2 (0.9–1.8)	1.0 (0.5–1.3)	0.097
CMT baseline (µM)	389.0 (299.0–466.0)	303.0 (250.0–442.0)	0.033
CMT post injection (µM)	257.0 (220.0–330.0)	335.0 (254.0–490.0)	0.002

Data are presented as the median (IQR) for continuous measures
Abbreviations: BCVA, Best Corrected Visual Acuity; CMT, central macular thickness; IQR, interquartile range.
Wilcoxon rank test was used to analyse all measurements of BCVA and CMT above.

The distribution of IL-1α genotypes according to demographic and clinical characteristics is presented in Table 3a. No homozygous risk allele carriers were identified in either response group. There were no significant differences in age, sex, BCVA, or CMT measurements across IL-1α genotypes in either responders or non-responders (P > 0.05 for all comparisons).

For IL-1β (Table 3b), the genotype frequencies were 12.8% for the non-risk (CC) genotype, 48.7% for heterozygous (CT), and 38.5% for the risk (TT) genotype. A significant association with sex was observed among responders (P = 0.021), with a higher proportion of females in the risk genotype group (87%) compared to the non-risk group (20%). Post-injection BCVA also differed significantly across genotypes (median 0.9 logMAR in CC, 1.6 in CT, and 0.7 in TT; P = 0.006). In contrast, demographic and clinical characteristics did not differ significantly across IL-1β genotypes in non-responders.

The T risk allele was more frequent among responders (62.8%) than non-responders (48.8%) (Table 4). The multivariable-adjusted logistic regression analysis showed that people having the T risk allele were more likely to be non-responders by 0.61 x (95% CI 0.32–1.16); without clinical significance (P > 0.05). Similarly, people carrying heterozygous genotypes (CT) and risk genotypes (TT) had 0.66 x (95% CI 0.15–2.88) and 0.33 x (95% CI 0.06–1.72) were expected to be non-responders, respectively. However, these differences were not statistically significant (P > 0.05).

Discussion

The primary finding of our genetic analysis indicates that IL-1α and IL-1β polymorphism had no significant association with anatomical response to anti-VEGF therapy in patients with nAMD. Although a non-significant trend was observed, with the IL-1β T allele being linked to a reduced likelihood of non-response (multivariable OR: 0.61; 95% CI 0.32–1.16), the results suggest that this polymorphism does not substantially influence short-term treatment outcomes with bevacizumab.

Inflammation and angiogenesis were highly affected by the IL-1 cytokine family, particularly IL-1α and IL-1β.[8] Polymorphisms in the IL-1β gene have been implicated in various conditions, including breast and prostate cancer, underscoring its broader role in pathological neovascularisation.[11,12] This pro-angiogenic function is further supported by its known activity in inducing vascular growth.[8] In Brazil, the IL-1β −31C/T and −511C/T polymorphisms have shown associations with primary open-angle glaucoma,[13] highlighting its potential significance in ocular disease. However, data on its role in nAMD, particularly in the Indonesian population, remains scarce.

It is noteworthy that elevated serum levels of IL-1α and IL-1β have been consistently reported in patients with AMD compared to controls (P = 0.02; 0.03).[14] IL-1α is also significantly linked to macular drusen (P = 0.008),[14] indicating its contribution in disease activity. However, the involvement of IL-1 gene polymorphisms in AMD pathogenesis or treatment response remains unclear.

Our findings align with several previous genetic studies. Tsai et al.[15] found that IL-1β −511 polymorphism was not significantly associated with nAMD, identifying IL-8 +781 C/T as the only interleukin gene among the four studied interleukin genes that had an association with wet AMD. Similarly, Makita et al.[16] reported that genotype proportions of the variant IL-1β rs1143627 were similar between patients with AMD and control in the Brazilian population.

Table 3a. Genotype distribution based on demographic and clinical data of IL-1α

	Responder			P	Non-responder			P
	Non-risk (CC) N = 33 (84.6%)	Hetero (CT) N = 6 (15.4%)	Risk (TT) N = 0 (0%)		Non risk (CC) N = 36 (83.7%)	Hetero (CT) N = 7 (16.3%)	Risk (TT) N = 0 (0%)	
Age	69.0 (65.0–76.0)	73.5 (65.0–78.0)	-	0.68#	65.0 (61.0–69.0)	62.0 (60.0–74.0)	-	0.75#
Sex				1.00^				0.67^
Male	11 (33%)	2 (33%)	-		12 (34%)	3 (43%)	-	
Female	22 (67%)	4 (67%)	-		23 (66%)	4 (57%)	-	
Pre injection logMAR BCVA	1.3 (0.9–1.8)	1.5 (1.0–1.8)	-	0.47#	1.1 (0.7–1.5)	1.0 (0.8–1.5)	-	0.89#
Post 1m injection logMAR BCVA	1.2 (0.9–1.8)	1.2 (0.8–2.1)	-	0.82#	1.1 (0.4–1.3)	1.0 (0.5–1.3)	-	0.93#
Pre injection CMT (µM)	389.0 (285.0–450.0)	403.0 (318.0–555.0)	-	0.44#	301.5 (251.0–404.5)	333.0 (247.0–551.0)	-	0.72#
Post 1m injection CMT (µM)	253.0 (220.0–329.0)	295.0 (243.0–398.0)	-	0.30#	335.5 (279.0–482.5)	328.0 (243.0–508.0)	-	0.77#

Data are presented as median (IQR) for continuous measures, and n (%) for categorical measures.
#Wilcoxon rank-sum
^Chi-square Test

Table 3b. Genotype distribution based on demographic and clinical data of IL-1β

	Responder			P	Non-responder			P
	Non-risk (CC) N = 5 (12.8%)	Hetero (CT) N = 19 (48.7%)	Risk (TT) N = 15 (38.5%)		Non-risk (CC) N = 12 (27.9%)	Hetero (CT) N = 20 (46.5%)	Risk (TT) N = 11 (25.6%)	
Age	75.0 (65.0–75.0)	76.0 (69.0–80.0)	67.0 (64.0–75.0)	0.11*	63.0 (61.0–69.0)	63.5 (60.5–68.5)	68.0 (63.0–72.0)	0.66*
Sex				0.021^				0.78^
Male	4 (80%)	7 (37%)	2 (13%)		4 (36%)	8 (40%)	3 (27%)	
Female	1 (20%)	12 (63%)	13 (87%)		7 (64%)	12 (60%)	8 (73%)	
Pre injection logMAR BCVA	1.0 (0.1–1.0)	1.5 (1.0–1.8)	1.3 (0.9–1.5)	0.19*	0.8 (0.7–1.1)	1.2 (1.0–1.6)	1.2 (0.7–1.8)	0.19*
Post 1m injection logMAR BCVA	0.9 (0.6–1.2)	1.6 (1.3–2.1)	0.7 (0.5–0.9)	0.006*	0.8 (0.5–1.3)	1.1 (0.5–1.3)	1.0 (0.4–1.5)	0.93*
Pre injection CMT (µM)	389.0 (340.0–597.0)	402.0 (343.0–515.0)	308.0 (252.0–450.0)	0.14*	301.5 (249.5–449.0)	302.0 (252.5–375.0)	349.0 (242.0–461.0)	0.98*
Post 1m injection CMT (µM)	298.0 (269.0–320.0)	257.0 (213.0–329.0)	231.0 (209.0–356.0)	0.65*	327.5 (271.5–509.0)	344.5 (287.0–445.0)	326.0 (247.0–490.0)	0.98*

Data are presented as median (IQR) for continuous measures, and n (%) for categorical measures.
*Kruskal-Wallis Test
^Chi-square Test

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This collective evidence is consistent with our primary result, where multivariable-adjusted logistic regression analysis showed that the response toward anti-VEGF treatment was not significantly affected by the IL-1β −511C/T polymorphism. In this study, circulating IL-1α and IL-1β levels were not measured; therefore, the analysis reflects genetic susceptibility rather than functional cytokine expression, which may partly explain the absence of a significant association between IL-1 polymorphisms and anatomical response to anti-VEGF therapy.

In summary, this study provides novel genetic data from an Indonesian cohort, utilising standardised anatomical criteria to evaluate the association between polymorphism of IL-1 gene and nAMD. Our analysis conclusively determined that the specific polymorphism of IL-1α and IL-1β did not serve as significant predictors of anatomical response to intravitreal bevacizumab. Although responders exhibited a significant decrease in CMT, this therapeutic effect was not modulated by the investigated genotypes in a statistically significant manner.

The biological plausibility of IL-1 involvement in AMD pathogenesis makes these null findings particularly important. Damage to the blood-ocular barrier and RPE leads to sustained cytokine production, including IL-1α and IL-1β.[17] As a pro-angiogenic factor, IL-1β acts by provoking VEGF secretion, thereby promoting CNV, while IL-1α contributes to RPE cell susceptibility to photooxidative damage.[18] Despite this compelling biological rationale, our results indicate that the specific polymorphisms of IL-1α −889C/T and IL-1β -511C/T did not significantly account for the variability in anatomical outcomes following bevacizumab therapy.

However, generalisability of these findings was limited by the retrospective design and modest sample size. This limitation also underscores the complexity of the genetic architecture underlying treatment response, suggesting that other inflammatory mediators or genetic loci may exert a more dominant influence. Future studies with greater sample size and prospective cohorts are warranted to further clarify the role of inflammatory gene polymorphisms in nAMD. Longitudinal assessment of both serum and intraocular cytokine levels, combined with comprehensive genotyping approaches, may provide a more robust understanding of the complex genetic and inflammatory mechanisms underlying treatment response to anti-VEGF therapy.

Conclusion

Our study showed IL-1α −889C/T (rs1800587) and IL-1β -511C/T (rs16944) gene polymorphisms did not significantly influence the response therapy for intravitreal bevacizumab in patients with nAMD, despite some parameters exhibits a significant change in IL-1β. However, our findings indicate a potential protective effect of the IL-1β -511C/T gene polymorphism against poor response to bevacizumab therapy, though statistical significance was not achieved. A greater sample size is necessary to validate the predictive value of IL-1 genetic variations for anti-VEGF treatment outcomes in nAMD patients in future studies.

Table 4. Genotype and allele frequencies and logistic regression analysis for IL-1β among responders vs. non responders

IL-1β	Responder N = 39	Non-responders N = 43	OR (95% CI)[1]	*P*	OR (95% CI)[2]	*P*	OR (95% CI)[3]	*P*
Allele	N(%)	N(%)						
Non risk (C)	29 (37.2%)	44 (51.2%)	reference		reference		reference	
Risk (T)	49 (62.8%)	42 (48.8%)	0.56 (0.30–1.05)*	0.07	0.59 (0.32–1.11)*	0.1	0.61 (0.32–1.16)*	0.1
Genotype								
Non risk (CC)	5 (12.8%)	12 (27.9%)	reference		reference		reference	
Hetero (CT)	19 (48.7%)	20 (46.5%)	0.44 (0.13–1.48)	0.2	0.51 (0.14–1.83)	0.3	0.66 (0.15–2.88)	0.6
Risk (TT)	15 (38.5%)	11 (25.6%)	0.31 (0.08–1.12)	0.07	0.29 (0.07–1.20)	0.1	0.33 (0.06–1.72)	0.2

Logistic regression using *logit* in STATA
[1] Crude OR (unadjusted logistic regression analysis)
[2] Adjusted OR (age and sex-adjusted logistic regression analysis)
[3] Multivariable-adjusted OR (age, sex, blood pressure, body mass index, and smoking-adjusted logistic regression analysis)
* Additive model using *haplologit* in STATA

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