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Research Article

Biological Determinants of Anti-VEGF Non-Responsiveness in Neovascular Age-Related Macular Degeneration and Diabetic Macular Edema

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Abstract

Background: The standard treatment for neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME) is anti-vascular endothelial growth factor (anti-VEGF) therapy; however, a considerable proportion of patients show an incomplete response. The aim of this study was to assess clinical, systemic, and optical coherence tomography (OCT)- based determinants of anti-VEGF non-responsiveness in patients with nAMD and DME in Babylon Province, Iraq. **Methods:** A hospital-based observational analytical study with a mixed retrospective-prospective design was conducted on 148 patients who received at least three intravitreal anti-VEGF injections. A consecutive sampling method was applied. Data included demographic characteristics, systemic diseases, best-corrected visual acuity (BCVA), and SD-OCT findings. Treatment response was classified into three categories: responders, partial responders, and non-responders. Categorical variables were compared using Pearson's chi-square test, while continuous variables were compared using one-way analysis of variance or the Kruskal-Wallis test, as appropriate. Independent predictors of treatment response were identified using multinomial logistic regression analysis. **Results:** Non-responders accounted for 31.8% of patients. There were significant differences between the three treatment response groups for baseline central macular thickness ($p<0.001$), diabetes duration ($p<0.001$), hypertension ($p=0.021$), persistent intraretinal fluid ($p<0.001$), hyperreflective foci ($p<0.001$), and ellipsoid zone disruption ($p<0.001$). Multivariate multinomial logistic regression analysis found that the duration of diabetes, baseline macular thickness, hypertension, hyperreflective foci, and ellipsoid zone disruption were independent risk factors for treatment response. **Conclusion:** Treatment response to anti-VEGF therapy varied according to several clinical and OCT characteristics. Diabetes duration, hypertension, baseline macular thickness, hyperreflective foci, and ellipsoid zone disruption independently predicted treatment response, supporting individualized management strategies.

1. Introduction

The principal causes of irreversible central vision loss in developed and developing populations are neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME), both of which are fundamentally driven by dysregulated vascular endothelial

growth factor (VEGF)- mediated vascular permeability and neovascular proliferation [1, 2]. The advent of intravitreal anti-VEGF agents has substantially transformed the therapeutic landscape of retinal vascular diseases, establishing VEGF inhibition as the standard of care and significantly improving visual prognosis across both conditions [2, 3].

Even with the excellent success observed in randomized clinical trials,–he 49% of patients who remain treatment-resistant and/or demonstrate an incomplete structural and functional response (fluid within/below the retina, poor vision response after multiple injections) [4] represent a considerable challenge for durable disease control and overall treatment success [5].

Multiple data indicate that non-responsiveness to anti-VEGF therapies can not be entirely due to drug resistance, but is actually the consequence of ongoing inflammatory stimulation and different signaling mechanisms for angiogenesis [6–8]. Ongoing vascular leakage that cannot be attributed to suppression of VEGF-A by either anti-VEGF agent for nAMD and DME was associated with elevated levels of other proangiogenic factors (e.g., Angiopoietin-2, platelet-derived growth factor [PDGF]) and inflammatory cytokines (e.g., Interleukin-6 and TNF-α) [9].

For nAMD, irreversible tissue remodelling and fibrotic transformation occur with continuous structural changes in the retinal pigment epithelium, thickness of Bruch's membrane, and worsening choroidal ischemia, meaning that the neovascular lesion will be only partially reversible by treatment [10]. However, the blood-retinal barrier in DME is due to metabolic inflammation and leukostasis and therefore reflects a microvascular disease on a systemic level, which does not entirely rely on VEGF signalling alone [11].

Inter-individual variability in therapeutic response, with polymorphisms in complement factor H, VEGF-A, and inflammatory regulatory genes being associated with differential anti-VEGF outcomes, is related to genetic susceptibility [12]. Moreover, systemic comorbidities such as chronic hyperglycemia, hypertension, and dyslipidemia aggravate retinal microvascular dysfunction, particularly in diabetic populations, thereby promoting persistent edema and reduced responsiveness to therapy [13].

The decline in therapeutic efficacy over time is related to biological factors, drug tolerance, and the phenomenon of accelerated response, and is likely due to loss of receptor sensitivity or increased regulation of alternative angiogenesis pathways [14]. The limitations of VEGF-focused therapy are highlighted by the responses of these adaptive biological factors, underscoring the need for multi-targeted or individualized therapeutic strategies [15]. Identifying predictive biomarkers and developing next-generation therapeutic approaches are linked to a deep understanding of these biological factors, both of which are essential for improving long-term visual outcomes. Therefore, this study aimed to investigate the biological factors underlying the lack of response to VEGF antagonists in neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME), with particular emphasis on angiogenic, inflammatory, genetic, and structural factors in the retina that contribute to suboptimal treatment outcomes.

2. Material and Methods

2.1. Study Design and Setting

A hospital-based observational analytical study with a mixed retrospective-prospective approach was designed to investigate clinically and imaging-derived biological determinants associated with anti-VEGF non-responsiveness in patients with neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME). The study was conducted in ophthalmology centers in Babylon Province, Iraq, which serve as referral facilities for retinal diseases and routinely provide intravitreal anti-VEGF therapy. The study design was purposefully aligned with the available diagnostic base structure in the local setting, where advanced molecular testing, genetic profiling, and vitreous biomarker assays are not routinely available. This precluded the study from being based solely on imaging-based and clinically determined markers, focusing mainly on spectral-domain optical coherence tomography (SD-OCT) and standard ophthalmic review as standard validated measures that represent surrogates of retinal disease activity internationally.

2.2. Study Sample

Adult patients with nAMD or DME presenting to retinal clinics and treated with anti-VEGF intravitreal therapy (faricimab, ranibizumab, aflibercept, or bevacizumab) according to the guidelines of care. Diagnosis was confirmed by standard clinical examination and SD-OCT scans identifying macular edema or neovascular activity. The main criteria for selection were the presence of documented OCT scans at baseline and one follow-up visit post-anti-VEGF initiation to allow analysis of patterns of response.

A consecutive non-probability sampling was applied. The sample size was obtained by enlisting all eligible patients who satisfied the inclusion criteria and attended the retinal clinics during the study period. In an environment where patient enrolment depends on patients attending the clinics, by referral is a widely used sampling frame for evidence of ophthalmology research rather than a population-based approach [16].

2.3. Sample Size

The sample size was estimated using a standard prevalence-based formula for an observational study with a conservative assumption of 30% prevalence from prior publications on retinal vascular diseases with roughly 25–30% anti-VEGF non-response rates. The estimated minimum sample size needed was approximately 126 patients for a 95% confidence interval with an 8% margin of error. An additional 15% were added for patients with incomplete records, those who did not receive a follow-up image, or those eliminated in data cleaning. Thus, the target sample size was approximately 145 patients. Ultimately, 148 patients were included and considered sufficient for the planned comparative and multivariate statistical analyses.

Patients were included in this study if they were 40 years of age or older with a documented diagnosis of nAMD or DME, received at least three consecutive intravitreal anti-VEGF injections, and possessed available baseline and follow-up SD-OCT scans. Patients with co-existing retinal vascular diseases, such as retinal vein occlusion, history of vitreoretinal surgery, high-degree glaucoma, media opacification causing poor image quality, and inadequate clinical and imaging data were excluded to avoid confounding anatomical and functional outcomes.

2.4. Data Collection

Data were gathered through structured medical record reviews and standardized clinical ophthalmic examinations. A retrospective portion collected demographic, diagnosis, treatment regimen, number of injections, and OCT findings from existing patient files. The prospective part collected post-treatment evaluations from newly recruited patients during follow-up cycles. The clinical evaluation consisted of measurement of best-corrected visual acuity using standard charts, slit-lamp biomicroscopy, IOP measurement, and dilated fundus examination. Systematic clinical information, such as duration of diabetes mellitus, hypertension, and HbA1c values (if mentioned in the file), was also collected. No further laboratory investigations, apart from those routinely offered as standard clinical care, were possible due to resource limitations.

2.5. Imaging Assessment

The primary imaging modality used for anatomical evaluation and biological inference was spectral-domain optical coherence tomography (SD-OCT). OCT parameters included central macular thickness, presence and persistence of intraretinal fluid, subretinal fluid, hyperreflective foci, and integrity of outer retinal layers, including the ellipsoid zone. They were not systematically included in the study protocol due to the limited availability of advanced imaging modalities, such as OCT-angiography and routine fluorescein angiography. Hence, as validated surrogate indicators of disease activity, vascular permeability, and tissue integrity, alongside established retinal research methodologies in resource-limited clinical environments, structural OCT biomarkers were used [17, 18].

2.6. Anti-VEGF Response

Based on combined anatomical and functional outcomes, the patients were classified into responder, partial responder, and non-responder groups. Patients demonstrating significant reduction or complete resolution of macular fluid on OCT with corresponding improvement in best-corrected visual acuity after anti-VEGF therapy were defined as responders. Patients with persistent intraretinal and/or subretinal fluid despite receiving at least three consecutive injections, accompanied by minimal or no improvement in visual acuity, were defined as non-responders. Patients who exhibited intermediate anatomical improvement without full resolution of fluid or complete functional recovery were defined as partial responders. This classification approach is consistent with widely used clinical response frameworks in retinal vascular disease studies [19].

2.7. Feasibility Indicators

The biological determinants were identified using only clinical and imaging indicators, due to the unavailability of molecular, genetic, and vitreous biomarker tests in Babylon. Vascular activity was indirectly inferred through the persistence of perfusion in optical coherence tomography (OCT) and recurrence of fluid after loading doses. The presence of diffuse retinal thickening and highly reflective foci in optical coherence tomography, which are known alternative indicators of inflammatory burden in retinal diseases, was used to assess inflammatory activity. Structural deterioration was assessed through disturbance of the elliptical zone, atrophy of the outer retina, and subretinal fibrosis. Using the documented clinical history of duration of diabetes, hypertension, and available glycated hemoglobin (HbA1c) values, the systemic metabolic impact was assessed, reflecting systemic vascular stress that contributes to the development of retinal diseases. The study design did not include any experimental or non-routinely available laboratory tests.

2.8. Ethical Consideration

The study protocol was approved by the Institutional Ethics Committee of the Associated Ophthalmology Center in Babylon. The study adhered to the principles of the Declaration of Helsinki. Informed consent was obtained from all pre-registered participants, and data confidentiality was maintained through anonymized data encryption and secure storage of patient records.

2.9. Statistical Analysis

Standard statistical software was used to perform data analysis. To summarize demographic and clinical characteristics, descriptive statistics were used. Continuous variables were reported as the mean SD and compared using a one-way analysis of variance (ANOVA) for variables that met the normality of distribution criteria or the Kruskal–Wallis test for variables that did not conform to the criteria. Variables that showed significance during the univariate analyses were introduced to a multinomial logistic regression model to detect predictors of treatment response independent of others. The significance level was set at $p < 0.05$.

3. Results

Table 1 shows that the average age of the patients was 63.4 ± 9.8 years and the average duration of diabetes was 11.6 ± 6.3 years. The majority of the patients were female (80 patients, 54.1%) compared to males (68 patients, 45.9%). Regarding the type of disease, patients with diabetic macular edema (81 patients, 54.7%) were the most affected, followed by patients with age-related macular degeneration (67 patients, 45.3%), then patients with diabetes (92 patients, 62.2%), and finally patients with hypertension (85 patients, 57.4%).

Table 2 shows that the majority of participants in the study were responders (n = 62, 41.9%), followed by non-responders (n = 47, 32.8%), and partial responders (n = 39, 26.4%).

Table 1: Baseline demographic and clinical characteristics (n=148)

Variable	Value
Age (years), mean± SD	63.4 ± 9.8
Gender (Male), n (%)	68 (45.9%)
Gender (Female), n (%)	80 (54.1%)
Disease type–nAMD, n (%)	67 (45.3%)
Disease type–DME, n (%)	81 (54.7%)
Diabetes mellitus, n (%)	92 (62.2%)
Hypertension, n (%)	85 (57.4%)
Mean duration of diabetes (years)	11.6 ± 6.3

Table 2: Anti-VEGF treatment response classification

Response category	n (%)
Responders	62 (41.9%)
Partial responders	39 (26.4%)
Non-responders	47 (31.8%)

Table 3 demonstrates the baseline clinical and OCT features of responders, partial responders, and non-responders to anti-VEGF therapy. There were statistically significant differences between the three treatment response groups in terms of age (p = 0.018), baseline central macular thickness (p <0.001), diabetes duration (p<0.001), hypertension (p = 0.021), and intraretinal fluid persistence (p<0.001). The non-responders showed poorer baseline characteristics than the responders, whereas the partial responders showed values intermediate between the two groups. These data support the idea of a gradual deterioration of the baseline condition from the responders through the partial responders to non-responders.

Table 3: Comparison of baseline clinical and OCT characteristics

Variable	Responders (n = 62)	Partial Responders (n = 39)	Non-Responders (n = 47)	p-value
Age (years), mean ± SD	61.2 ± 8.7	65.9 ± 10.2	65.9 ± 10.2	0.018*
Baseline CMT (μm), mean ± SD	412 ± 86	498 ± 102	498 ± 102	<0.001*
Diabetes duration (years), mean ± SD	9.4 ± 5.1	14.2 ± 6.8	14.2 ± 6.8	<0.001*
Hypertension, n (%)	48.4%	70.2%	33 (70.2%)	0.021†
Persistent IRF, n (%)	22.6%	78.7%	37 (78.7%)	<0.001†

Table 4 Distribution of structural OCT biomarkers in responders, partial responders, and non-responders after anti-VEGF therapy. OCT biomarkers were significantly different between responders, partial responders, and non-responders for all assessed OCT markers. The frequency of hyperreflective foci, disruption of the ellipsoid zone, persistent subretinal fluid, outer retinal atrophy, and subretinal fibrosis progressively rose from responders, through partial responders, to non-responders. These results suggest that increasing degrees of retinal structural damage seen on OCT correlate with decreased response to anti-VEGF therapy and that these OCT biomarkers might have a value in predicting resistance to anti-VEGF therapy.

Table 4: OCT-derived structural biomarkers

OCT-derived structural biomarker	Responders (n=62) (%)	Partial Responders (n=39) (%)	Non-Responders (n=47) (%)	p-value
Hyperreflective foci	32.3	74.5	74.5	<0.001†
Ellipsoid zone disruption	29.0	68.1	68.1	<0.001†
Persistent subretinal fluid	25.8	61.7	61.7	0.002†
Outer retinal atrophy	19.4	57.4	57.4	<0.001†
Subretinal fibrosis	11.3	46.8	46.8	<0.001†

The multivariate logistic regression analysis in Table 5 shows that the duration of diabetes is associated with non-response to treatment with vascular endothelial growth factor antagonists (odds ratio = 1.18, 95% confidence interval: 1.07-1.31, p-value = 0.001). Regarding the thickness of the central molecular layer at baseline, the study revealed a significant correlation with non-response (odds ratio = 1.02, 95% confidence interval: 1.01-1.03, p-value < 0.001). Regarding high blood pressure, the study revealed a significant association with non-response (odds ratio = 2.14, 95% confidence interval: 1.08-4.22, p-value = 0.029). Regarding the elliptical region disorder, the study revealed a significant association with non-response (odds ratio = 3.67, 95% confidence interval: 1.74-7.74, p-value < 0.001). Regarding highly reflective foci, the study revealed a significant association with non-response (odds ratio = 2.89, 95% confidence interval: 1.38-6.05, p-value = 0.05).

Table 5: Independent predictors of anti-VEGF non-responsiveness

Predictor	Adjusted OR	95% CI	p-value
Diabetes duration	1.18	1.07–1.31	0.001
Baseline CMT	1.02	1.01–1.03	<0.001
Hypertension	2.14	1.08–4.22	0.029
Ellipsoid zone disruption	3.67	1.74–7.74	<0.001
Hyperreflective foci	2.89	1.38–6.05	0.005

Table 6 shows that the majority of patients with age-related macular degeneration (nAMD) responded to treatment (n = 31, 46.3%), followed by partial responders, and then non-responders (n = 18, 26.8%). For patients with DME, most of them responded to treatment (n = 31, 38.3%), followed by non-responders (n = 29, 35.8%), and then partial responders (n = 21, 25.9%). This difference in distribution was statistically significant (p = 0.041).

Table 6: Response distribution by disease type

Disease type	Responders	Partial responders	Non-responders	p-value
nAMD (n=67)	31 (46.3%)	18 (26.9%)	18 (26.8%)	0.041
DME (n=81)	31 (38.3%)	21 (25.9%)	29 (35.8%)	

4. Discussion

The present study reveals that approximately one-third of patients with neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME) were classified as non-responders to anti-VEGF therapy (31.8%). This non-response rate was comparable to the results of observational studies, which showed that 25–45% of patients develop incomplete anatomic and functional responses after repeated intravitreal injections [20]. However, in the context of a well-monitored and highly selective population (stricter entry criteria, protocol-specified outcome measures), high responders are typically much higher in key randomized controlled trials, which indicate that patient factors are a key determinant of the treatment response [21]. In the view of the researcher, the results of this study are better represented in the observational rather than randomized controlled trial, in terms of capturing heterogeneity seen in clinical practice.

The current findings demonstrated a statistically significant association between baseline central macular thickness (CMT) and anti-VEGF non-responsiveness (498 ± 102 μm in non-responders compared to 412 ± 86 μm in responders, p-value < 0.001). Another similar finding was obtained by Chakravarthy et al. The persistence of fluid and poor anatomical response to anti-VEGF treatment correlated with greater baseline macular thickness [22]. From the authors' view, the excess macular thickening found in severe stages reflects increased vascular leakage burden and structural macular disruption, which may surpass the effectiveness of VEGF inhibition alone.

The study also revealed that longer diabetes duration was significantly associated with non-responsiveness (14.2 ± 6.8 years in non-responders compared to 9.4 ± 5.1 years in responders, p-value < 0.001) and remained an independent predictor in regression analysis (OR = 1.18, p-value = 0.001). This finding was supported by Usui-Ouchi et al., who reported more severe microvascular damage and reduced response to anti-VEGF therapy in DME related to prolonged diabetes duration [23]. However, studies have found that the stronger determinant of treatment response is glycemic control rather than disease duration [24, 25]. From the researcher's perspective, the results of structural changes that are less reversible even after VEGF suppression, related to prolonged exposure to hyperglycemia, lead to cumulative endothelial dysfunction, capillary dropout, and chronic inflammatory activation.

Persistent intraretinal fluid was markedly higher in non-responders (78.7% compared to responders 22.6%, p-value < 0.001), this finding was alongside a study by Asadi Khameneh et al., who reported that the key indicator of treatment resistance and disease chronicity was the persistent fluid after anti-VEGF therapy [26]. From the researcher's perspective, the point of view that more complex disease mechanisms beyond simple VEGF-mediated permeability will occur due to persistent fluid in this study reflects ongoing pathological vascular leakage driven by VEGF-independent pathways.

Concerning OCT biomarkers, hyperreflective foci were significantly more frequent in non-responders (74.5% compared to responders 32.3%, p-value < 0.001). This finding was alongside a study by Fragiotta et al., who identified that poorer treatment response was related to hyperreflective foci as a marker of inflammation and lipid-laden macrophage infiltration [27]. From the researcher's point of view, the increased presence of hyperreflective foci reflects chronic inflammation and lipid extravasation, which leads to persistent retinal edema and reduced responsiveness to anti-VEGF therapy.

Ellipsoid zone disruption was also significantly associated with non-responsiveness (68.1% compared to responders 29.0%, p-value $<$ 0.001) and was considered the strongest independent predictor in the regression analysis (OR = 3.67, p-value < 0.001). This finding was in accordance with the results reported by Chen et al., who demonstrated that the critical determinant of functional recovery in retinal vascular diseases is outer retinal integrity [28]. From the researcher's perspective, ellipsoid zone disruption reflects irreversible photoreceptor injury, thereby limiting the potential for visual recovery even when exudation is controlled.

Subretinal fibrosis was significantly more frequent in non-responders (46.8% compared to responders 11.3%, p-value < 0.001). This finding was alongside a result reported by Zhao et al., who reported that an advanced stage of neovascular disease with poor therapeutic reversibility is associated with fibrotic transformation [29]. However, early intervention studies suggest that timely anti-VEGF therapy could prevent fibrosis [30]. From the researcher's point of view, fibrosis represents end-stage tissue remodeling driven by chronic inflammation and sustained neovascular activity, which is largely unresponsive to VEGF alone.

The study demonstrated that DME patients had a higher proportion of non-response than nAMD patients (35.8% vs. 26.8%, p = 0.041). This finding, alongside a result conducted by Parravano et al., who reported that systemic metabolic and inflammatory influences cause DME, shows more heterogeneous and incomplete response patterns [31]. However, another study reported comparable response rates between both conditions when treated with aflibercept [32]. From the researcher's point of view, DME is less uniformly responsive to monotherapy targeting VEGF alone because it is driven by both VEGF-dependent and VEGF-independent inflammatory pathways.

Study Limitations

This study suffers from the limited ability to generalize its results to wider population groups with different healthcare systems and demographic characteristics because it was conducted in one area in the Babylon Governorate of Iraq. The lack of advanced diagnostic tools, such as optical coherence tomography (OCT) angiography, genetic testing, and molecular biomarker assays, has limited the assessment of biological determinants to clinical evaluation and high-resolution SD-OCT, making it difficult to rely on alternative, indirect, imaging-based indicators instead of direct biological measurements. In addition, selection bias will occur in the non-probability sequential sampling method as a result of overrepresenting patients with better follow-up adherence, whereas retrospective data collection may have resulted in a lack or incompleteness of clinical information. The short follow-up period may not fully reflect the variability in long-term treatment response, and the presence of residual confounding factors due to unmeasured factors, such as genetic predisposition and inflammatory status, cannot be ruled out.

5. Conclusion

One-third of patients affected by anti-VEGF non-responsiveness in neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME) are relatively common phenomena in clinical practice and reveal significant associations with higher baseline central macular thickness, longer diabetes duration, systemic hypertension, and specific OCT structural biomarkers such as hyperreflective foci and ellipsoid zone disruption. These findings indicate that the combination of systemic vascular factors and retinal structural damage will influence the treatment response rather than VEGF-mediated activity alone. Therefore, to improve therapeutic outcomes, clinicians should adopt a more individualized treatment approach incorporating detailed OCT-based structural assessment and systemic disease optimization, especially glycemic and blood pressure control. Furthermore, to better elucidate the underlying mechanisms of resistance and to support the development of more targeted therapeutic strategies beyond VEGF inhibition, researchers recommend using large-scale, multicenter studies incorporating advanced imaging modalities and molecular biomarkers.

Article Information

Ethical Approval: The study was approved by the Ethics Committee of the Babil Health Directorate under approval number IEC/2024/012.

Informed Consent: Written informed consent was obtained from all participants before their inclusion in the study.

Data Availability: The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of Interest: The author declare that they have no conflict of interest.

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